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Synthetic Studies Towards the Total Synthesis of the Neocarzinostatin Chromophore

University College London

Olivier Thominet
Submitted for PhD
June 2007
Statement

I hereby declare that this thesis has not been submitted, either in the same or different form, to this or any other University for a degree.

Signature:

Olivier Thominet.

June 2007
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I would like to thank my supervisor Prof. Steve Caddick for his encouragement, enthusiasm and advice throughout my PhD. I am also grateful to Steve for having believed in my capabilities to work on this difficult project, for giving me the opportunity to write up a paper and for all other help towards making my PhD successful.

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Abstract

The chromoprotein Neocarzinostatin (NCS) was the first isolated member of the so-called ‘enediyne’ class of antibiotics and was found to exhibit broad-spectrum antitumor activity. NCS was isolated in 1965 from the bacterium *Streptomyces carzinostaticus* and is made up of a 1:1 non-covalent complex of an extraordinarily reactive nine-membered ring epoxydiyne chromophore (NCS-C) tightly bound to a protein known as apo-NCS. The antitumor activity arises solely from the chromophore which acts as a DNA-cleaving agent initiated by radical hydrogen abstraction of a deoxyribose residue. The apoprotein protects, carries and delivers the chromophore offering potential as a novel, more selective drug delivery system.

Our general strategy towards NCS-C involves the Michael addition of an epoxydiyne to a cyclopentenone followed by cyclisation via an aldol reaction. The enantioselective synthesis of the cyclopentenone fragment had already been synthesised within the group via enzyme-mediated kinetic resolution. The aim of this project is to report our current efforts to establish a general method for the synthesis of epoxydiynes in order to apply our own Michael/aldol sequence. Different routes to these epoxydiynes have been developed using a Sharpless asymmetric epoxidation. However, these have proven to be extremely difficult due to the formation of unstable intermediates which could not be processed to fully elaborated epoxydiynes. After considerable investigation, a concise and convergent approach to epoxydiynes was finally achieved on a multi-gram scale. This involves a diastereoselective addition of an allenyl zinc bromide to propargylic ketones/aldehydes followed by epoxide formation. This new protocol enables us to synthesise fully functionalised and stereochemically pure epoxydiynes including C-8 provides a very simple synthetic route to other functionalised epoxydiynes. Owing to the flexibility of our new method, epoxydiynes with different protecting groups can now be readily prepared enabling us to screen them in new Michael addition reaction studies.
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Abbreviations

A: deoxyadenosine
Ac: acetate
Aca: acetylacetonate
C: carbon atom
Cat: catalytic
CDI: carbonyldiimidazole
CDR: complementarity determining regions
Co₂CO₆: dicobalthexacarbonyl
Co₂CO₈: dicobaltoctacarbonyl
CSA: 10-camphorsulfonic acid
Cys: cysteine
Da: dalton
DABCO: 1,4-diazabicyclo[2.2.2]octane
Db: dibenzylideneacetone
DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene
DCC: 1,3-dicyclohexylcarbodiimide
DCE: dichloroethane
DCM: dichloromethane
DDQ: 2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEI: diethylisopropyl
DET: diethyl tartrate
(DHQD)₂PYR: 1,4-bis(9-O-dihydroquinidine)-diphenylpyrimidine
DIBAL: diisobutylaluminium hydride
DIPEA: N,N-diisopropylethylamine
DMAP: dimethylaninopyridine
DMF: N,N-dimethylformamide
DMP: Dess-Martin periodinane
DMSO: dimethylsulfoxide
DNA: deoxyribonucleic acid
E: Entgegen
EDC: 1-ethyl-3-[3-dimethylaminopropyl]carbodiimide
<table>
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<tr>
<th>Abbreviation</th>
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<tr>
<td>Gly</td>
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<tr>
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</tr>
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<td>HMDS</td>
<td>hexamethyldisilazide</td>
</tr>
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<td>high resolution mass spectroscopy</td>
</tr>
<tr>
<td>iPr</td>
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</tr>
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<td>Neocarzinostatin chromophore</td>
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</tr>
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<td>SAE</td>
<td>Sharpless asymmetric epoxidation</td>
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<td>---------------------</td>
<td>--------------------------------------------------</td>
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<tr>
<td>Ser</td>
<td>serine</td>
</tr>
<tr>
<td>SMANCS</td>
<td>poly(styrene-co-maleic acid/anhydride) Neocarzinostatin</td>
</tr>
<tr>
<td>T</td>
<td>deoxythymidine</td>
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<td>tetrabutylammonium fluoride</td>
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<td>TBHP</td>
<td>tert-butylhydroperoxide</td>
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<td>TBDPS</td>
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1 INTRODUCTION

1.1 Introduction

The chromoprotein Neocarzinostatin$^1$ (NCS or holo-NCS) is the first representative of a chemical class of antibiotics with broad-spectrum antitumour activity. NCS was found to have anti-proliferative properties against solid-tumor cell lines. NCS is made up of a 1:1 non-covalent complex of an extraordinary reactive nine-membered ring epoxydiyne chromophore (NCS-C) tightly bound to a protein known as apo-NCS (Figure 1).

*Figure 1. NCS (or holo-NCS): NCS-C + apo-NCS.*

The antitumour activity arises from the chromophore that acts as DNA-cleaving agent following activation by a thiol. The apoprotein protects, carries and delivers the chromophore to DNA.
1.2 History of NCS

In 1956, Ishida’s laboratory were focused on screening antitumour agents from *Streptomyces* culture broths. During this time Carzinostatin was discovered by Shoji from *Streptomyces E-743*, a soil bacteria harvested in Sendai, Japan and was found to possess curative effects on mice bearing tumours as well as an antibiotic activity against *Lutea sarcina*.² Shoji clearly established that carzinostatin consists of two components A and B. The antitumour activity was only efficient if both A and B were administered. B (probably a chromophore) is highly labile but its stability is recovered in the presence of A (probably an apoprotein). Carzinostatin was technically difficult to analyse and only few biological studies were carried out.² It is structurally different from NCS-C.

In 1964, Ishida et al. discovered NCS, a proteinaceous substance, from a culture filtrate of *Streptomyces carzinostaticus* Var. F-41, a mutant of the strain E-743 using *Sarcina lutea* as bio-assay.³ Neocarzinostatin was originally found to have an anti-proliferative effect against Ascitic leukaemia and Sarcoma 180 in mice with an impressive therapeutic index.³ In 1966, the protein (apo-NCS) was isolated from lyophilised NCS and Ishida already suspected the presence of a non-peptidic component.⁴ In 1972, Maeda et al. published the primary sequence of the protein⁵ which was revised⁶ and then confirmed later by NMR.⁷ NCS was used clinically to treat patients with leukaemia, gastric cancer and pancreatic cancer in 1977.⁸ NCS was initially identified as a protein and it was not until 1979 that NCS-C was finally discovered.⁹ In 1980, Goldberg et al. found that NCS-C undergoes rapid decomposition at high pH and upon incubation with thiols.¹⁰ In 1985, Edo et al. finally disclosed the relative structure of NCS-C.¹¹ In 1987, Myers proposed a mode of activation of NCS-C through chemical modification using a thiol adduct of the chromophore¹² and determined the assignment of its absolute configuration in 1988 as that of 1 (Figure 2).¹³
In 1993, Teplyalov et al. and Myers et al. crystallised respectively apo-NCS and holo-NCS. In 1994, Myers et al. observed a cumulene intermediate at low temperature by NMR spectroscopy and established a mode of activation of NCS-C at the molecular level. The same year, a polymer conjugated version of NCS SMANCS/lipodiol was approved by the ministry of health and welfare in Japan. Myers achieved the first total synthesis of the NCS-C in 1998, followed by Hirama in 2006.

1.3 Role of the NCS-C moieties

In the absence of its binding protein, NCS-C is highly sensitive to light, heat, elevated pH, nucleophiles, and readily cycloaromatises to generate a diradical species. Structurally, NCS-C consists of subunits which play key biological roles (Figure 3):

a) The naphthoate is responsible for much of the strength of the binding of the chromophore with the protein and it also acts as a DNA intercalating agent.

b) The sugar residue, N-methyl-fucosamine, plays an anchor-like role by forming electrostatic interactions with the negatively charged DNA phosphodiester bridge in the major groove hence, positioning the epoxydiyne core in the DNA minor groove. Myers et al. suggested that it also plays a key role in the activation of the chromophore by acting as an internal base in the thiol-activation pathway. The sugar residue of the NCS-thioglycolate adduct adopts a chair conformation with the amine functionality oriented above C12 approximating the Van der Waals diameter of
Lastly, the carbohydrate provides a stabilising effect on the chromophore core protecting C12 from thiol attack in solution. The highly reactive epoxybicyclo[7,3,0]dodecadiyne is responsible for the cytotoxic activity following nucleophilic activation. A subsequent Bergman-type rearrangement produces diradical species which abstracts a hydrogen atom from DNA resulting in single and double-stranded breaks.

d) The cyclic carbonate takes part in the passage of the NCS-C through cellular and nuclear membrane.

**Figure 3. Biological role of the NCS-C.**

### 1.4 Mode of activation

NCS-C exists in a pro-drug state and requires activation via nucleophilic addition to exert its cytotoxicity. Myers et al. established the precise mechanism for NCS-C activation at the molecular level (Figure 4). The activation cascade is triggered by a Michael-like addition of a thiol to the naphthoate at C12 in a *trans* manner. This leads to epoxide ring opening and the formation of a highly reactive cumulene intermediate 2 which undergoes a radical Myers-Saito cycloaromatisation to form the biradical 3. 3 cleaves DNA in a single and double stranded manner by radical hydrogen abstraction on the deoxyribose residue leading to the formation of 4 and DNA fragments.
Figure 4. Thiol-dependant mechanism of activation.

Goldberg et al. alternatively proposed a base-catalysed thiol independent mechanism (Figure 5).\textsuperscript{30} The activation begins by intramolecular Michael addition at C12 from the enolate at C1" of the naphthoate leading to the spirolactone cumulene 5. Myers-Saito cycloaromatisation then leads to the spirolactone (σ,σ)-1,4-diradical 6. The radical at C2 is then quenched by C8" to give the spirolactone (σ,π)-1,4-diradical 7 which abstracts hydrogen atom from particular DNA segments forming bulges to afford 8.
Figure 5. Base-catalysed thiol independent mechanism of activation.
1.5 DNA cleavage mechanism

The proposed DNA cleavage mechanisms have been supported with evidence from electrophoretic analysis of the DNA fragments generated. It has been demonstrated that at least 80% of the DNA cleavage leads to the 5'-aldehyde of the A and T residues selectively. The cleavage is initiated by radical pro-S $H$-abstraction from C5' of the deoxyribose residue 9. The resulting radical 10 is then trapped at C5' by O$_2$ coming from the major groove in anti fashion. The resulting peroxyradical 11 undergoes a thiol reduction via 12 that leads to strand cleavage and the formation of the 5' aldehyde-ended fragment 13 (Figure 6).

![Diagram of DNA cleavage mechanism]

Figure 6. DNA cleavage mechanism.

Less than 20% of the strand breaks result from pathways initiated by hydrogen atom abstraction from C4' and C1'.
1.6 holo-NCS

holo-NCS is made up of a 1:1 complex of a highly reactive chromophore, NCS-C, tightly bound to a protein known as apo-NCS (Kd = 0.1nM).\textsuperscript{32} Myers \textit{et al.} have reported the crystal structure of holo-NCS in 1993.\textsuperscript{15} The 2 \pi faces of the nine membered ring are sandwiched between Phe78 on one side and Phe52 and the Cys 37-Cys47 disulfide bond on the other. The epoxide faces down into the hydrophobic binding pocket preventing access from the solvent and subsequent ring opening. The aminosugar moiety is protonated and stacks against the Phe78 with partial contact with the solvent. The naphthoate lies in the bottom of the cleft and is involved with hydrogen-bonding interactions, for example the carbonyl group with the hydroxyl side chain of Ser98, and the methoxy group with the NH of Gly35. holo-NCS represents a particular protein/ligand interaction in that the carrier protein controls the release of its chromophore. In the crystal structure, only the orientation of Phe78 side chain shows a significant difference between holo- and apo-NCS structures. Furthermore, mutation studies using recombinant apo-NCS mutated on the Phe 78 exhibit an increase in the release rate of the chromophore.\textsuperscript{33} This suggests that the releasing mechanism potentially involves the side chain of Phe 78. It is not clear whether holo-NCS enters the cell and delivers the chromophore to DNA or whether it releases the chromophore at the cell surface. \textit{In vitro} inhibition experiments using agarose covalently immobilised NCS against leukemic human cell have shown that the released chromophore can enter the cell and reach the nucleus.\textsuperscript{34} Alternatively, fluorescent holo-NCS can be detected in the cytoplasm as well as the nucleus of human cells.\textsuperscript{35} Further fluorescence studies have shown that holo-NCS is readily taken up by \textit{Saccharomyces cerevisiae} and triggers the overexpression of DNA-repairing genes.\textsuperscript{36}

1.7 SMANCS

The potent cytotoxicity of NCS surpasses that of the widely used antitumour agents 5-fluorouracil, adriamycin and \textit{cis}-platinum at their minimum effective concentrations.\textsuperscript{37} NCS can inhibit tumour cell growth at the nM range, whereas many
of the low-molecular weight do so at the μM or mM range. However, the major limitations to the clinical use of NCS is its high toxicity towards healthy organs and its very short in vivo half life ($t_{1/2}$~1.9 min) in mice which require controlled infusion to increase plasma concentration and less systemic toxicity. These limitations were partially solved by the use of SMANCS, a polymer conjugated version of NCS. This is prepared by cross-linking the apo-NCS with two chains of poly(styrene-co-maleic acid/anhydride) (SMA) via its residues alanine 1 and lysine 20 (Figure 6). The polymer conjugation does not alter the biological activity of NCS.

![Chemical structure of SMA and SMANCS](image)

**Figure 7.** Chemistry of SMANCS.

SMANCS exhibits an in vivo half-life 10 times longer than that of NCS and reduces its immunogenicity. It preferentially targets solid tumour via a mechanism known as Enhancement Permeability and Retention (EPR). Hypervascularity surrounding the solid tumour increases the permeability towards SMANCS and limits its clearance via
the lymphatics. These major differences between the healthy tissue and tumour tissue contribute to the selective accumulation of SMANCS in tumours and hence, its increased efficacy over NCS alone. The clinical use of SMANCS has been approved by the Ministry of Health and Welfare in Japan in 1994 for treatment of liver, bladder, lungs, kidneys and brain cancer. Some recent applications of SMANCS have been reported.\textsuperscript{37,38} In the case of hepatoma, arterial administration of SMANCS through catheter decreased tumour size in 90\% of patients. A patient receiving such treatment might expect to have a 90\% chance of survival after treatment for at least 5 years for a controlled hepatoma.

1.8 apo-NCS

apo-NCS (11,000 Da) consists of 113 amino-acid residues with two disulfide bridges between Cys37-Cys47 and Cys72-Cys87. The three dimensional structure was determined by NMR\textsuperscript{39,40} and X-ray crystallography.\textsuperscript{14} The largest domain consists of a seven-stranded antiparallel $\beta$ sandwich formed by an external three-strand and an internal four-strand $\beta$-sheet. The smaller domain is composed of two-stranded $\beta$-ribbons perpendicular to each other. The internal $\beta$-sheet, the smaller domain and the helix loop between Asp48 and Phe52 define a deep hydrophobic U-cleft in which the chromophore is encapsulated. apo-NCS displays the same overall fold as immunoglobulin. apo-NCS protects, transports and delivers directly or indirectly the chromophore to its target, the DNA. The protein represents therefore a potential in generating a new drug delivery system as well as in targeting tumours more selectively. The NCS-C binding pocket was found to bind ethidium bromide,\textsuperscript{41} the antitumour agent daunomycin\textsuperscript{40} and naphthoate analogues of NCS-C.\textsuperscript{42} Caddick \textit{et al.} have used the natural naphthoate to anchor nitrogen mustards of therapeutic interest in the binding cleft with promising results.\textsuperscript{43} They also discovered flavones as efficient apo-NCS binders in the $\mu$M range.\textsuperscript{44} This opens up possibility of transporting covalently bound flavone-chemotherapeutic constructs using apo-NCS and allowing their controlled release. Minard \textit{et al.} have extended the binding properties of apo-NCS \textit{via} directed evolution on residues located in the binding cleft.\textsuperscript{45} The resulting apo-NCS mutant was found to bind testosterone and streptavidin bound testosterone at the $\mu$M and nM range respectively. They also attempted to find new recognition
capabilities by exchanging the immunoglobulin CDR-like loop by the CDR3 loop of the camel antilysozyme immunoglobulin. The newly engineered apo-NCS was able to bind lysozyme. These interesting results suggest that engineered apo-NCS is potentially able to transport various chemotherapeutics and also to target selectively proteins present at the surface of tumour cells.

1.9 Studies towards the synthesis of the NCS-C core structure

Hirama et al. have reported the synthesis of a NCS-C-related analogue using a highly functionalised iodo-cyclopentenone 15 including C8 and the epoxydiyne 16. Sonogashira coupling leads to 17 and then desilylation and DIBAL reduction afforded the aldehyde 18 which undergoes LHMDS/CeCl₃ promoted ring closure at C7-C8 to give the NCS-C core 19 (Scheme 1).

![Scheme 1. Synthesis of the NCS core structure via 1,2-addition.](image)

In 1991, Magnus et al. pioneered a successful strategy for the construction of a related-NCS core structure adopting a boron/cobalt-mediated aldol reaction in which
the epoxide at C4-C5 is surprisingly left untouched (Scheme 2). The synthesis begins with a coupling of iodo-alkene 21 and the cyclopentenone derivative 20 under Sonogashira conditions to give 22. Epoxidation of 22 using Sharpless asymmetric epoxidation followed by alcohol protection lead to the epoxydiyne derivative 23. Complexation of the less hindered C6-C7 alkyne bond with Co\textsubscript{2}CO\textsubscript{6} followed by hydrolysis of the activated diethyl acetal affords 24. Subsequent cobalt-mediated aldol reaction at C8-C9 under Lewis acid conditions followed by oxidative decomplexation lead to the NCS core analogue 25.

![Scheme 2. Synthesis of the NCS-C core via cobalt-mediated aldolisation.]

1.10 Myers’ total synthesis of the NCS-C

1.10.1 NCS-C model studies

Myers et al. have reported an enantioselective synthesis of the epoxydiyne core of the NCS-C. Their synthesis requires the preparation of the unsymmetrical epoxydiyne fragment 28 via a double palladium cross-coupling from ethyl-2,3-dibromopropenoate 26, followed by a selective desilylation of 27, a SAE and alcohol protection (Scheme 3).

Addition of the fragment 28 to the cyclopentanone 29 followed by sulfoxide formation/elimination and desilylation lead to 30. This is followed by acetal hydrolysis, silylation of the tertiary hydroxyl group and LHMDS/CeCl₃ mediated ring closure to give the NCS-C core intermediate 31. The olefin formation at C1-C12 and C8-C9 are achieved from 31 via acid-catalysed allylic transposition. Accordingly, silylation and treatment with TFA afford 32 which undergoes trifluoroacetate hydrolysis and protective group adjustment followed by a methanesulfonic acid anhydride/pyridine-mediated alcohol elimination at C8 to give 33 (Scheme 4).²⁴

Scheme 4. Synthesis of the NCS core via 1,2-addition followed by allylic transposition.
1.10.2 Total synthesis

Myers et al. have also reported the first complete total synthesis of the NCS-C.\textsuperscript{17, 51} Their strategy involves the convergent assembly of four components: a naphthoate, an epoxydiyne, a cyclopentenone and a carbohydrate. The epoxydiyne 39 was prepared in 9 steps from D-glyceraldehyde 34. The route includes a diastereoselective Wittig olefination (35→(E)-36), protective group manipulations (36→37), a primary alcohol silylation followed by Sharpless asymmetric epoxidation (37→38) and a selective silyl cleavage/diol protection affording 39 (Scheme 5).\textsuperscript{51}

![Chemical diagram](image)

Scheme 5. Synthesis of a key epoxydiyne.

The cyclopentenone (+)-41 was prepared in a one-pot procedure from the well known prostaglandin intermediate (+)-40\textsuperscript{52} via a carefully optimised application of the method of Noyori et al.\textsuperscript{53} In order to include C8 onto 40, trimethylsilylphenyl
selenide, trimethyl orthoformate and hydrogen peroxide/pyridine were sequentially added affording 41 in good yield (Scheme 6).


The naphthoate 44 was prepared from 4-bromo-3-methylanisole 42 in six steps in ~40% overall yield. The synthesis features the photocyclisation of 43 followed by a saponification to give 44. (Scheme 7).

Scheme 7. Synthesis of the naphthoate via photocyclisation.

The N-methylamino sugar donor 46 was synthesised in a 10 steps sequence from trio-O-acetyl-D-galactal 45 (Scheme 8). The sugar was activated as a Schmidt trichloroacetimidate for its high reactivity and its α-selectivity.

Scheme 8. Activation of the sugar residue via Schmidt trichloroacetimidate.
The fragments were then combined towards the synthesis of the NCS-C (Scheme 9). However problems occurred when trying to induce the allylic alcohol transposition and this strategy was abandoned. 1,2-addition of the epoxydiyne 39 to the cyclopentenone derivative 41 and further transformations led to the adduct 47. Subsequent asymmetric epoxidation and alcohol oxidation give 48 with the introduction of the stereocenter at C10-OH, the site of the impending glycosylation. Cerium-mediated ring closure to form the C7-C8 bond led to the NCS core analogue 49. Following protective group manipulations, the naphthoate group at C11-OH is installed via DCC-mediated esterification to afford 50. Carbonate incorporation after diol deprotection followed by selective silylation, C12-C1 olefin formation using the Martin sulfurane dehydrating agent and subsequent desilylation lead to 51. Epoxide ring opening and concomitant dehydration under PPh3/I2 conditions affords the NCS-C aglycon 52 in 15-30% yield. Lastly, the sugar residue is coupled at C10-OH via Schmidt glycosylation to provide exclusively the required α-anomer intermediate which is fully deprotected in one step to give NCS-C.
Scheme 9. Total Synthesis of the NCS-C.
1.11 Hirama's formal total synthesis of the NCS-C

Hirama et al. have recently reported the synthesis of the NCS aglycon in 2006. They\textsuperscript{18} Their strategy relies on an acetylide/aldehyde ring closure at C5-C6 leading to the core structure of NCS-C (Scheme 10). Key steps in the synthesis involves 1) A Sonogashira coupling between a functionalised iodo-cyclopentenone 53 and the acetylenic precursor 54\textsuperscript{57} followed by tertiary alcohol protection to afford 55; 2) The addition of propargylmagnesium bromide to 55 affording 56 as a separable diastereoisomeric mixture in a 1.2:1 ratio respectively; 3) Protective group manipulations, reduction/oxidation sequence and a diastereoselective LHMDS/CeCl\textsubscript{3} mediated ring closure to give 58 with the required trans geometry at C4-C5; 4) Introduction of the α-epoxide via mesylation/desilylation and base mediated ring closure (58→59). Lastly, naphthoate\textsuperscript{58} and carbonate installation (59→60), protective group manipulations (60→61), C8-C9 olefin formation using Martin sulfurane dehydrating reagent\textsuperscript{56} from 61 and controlled desilylation lead to the NCS-C aglycon 52.
Scheme 10. Total synthesis of the NCS-C.

The first total synthesis of N1999-A2, a structurally related NCS-C natural product, was also accomplished earlier via the same strategy. ⁵⁷
1.12 Total synthesis of the N1999-A2

N1999-A2 is a NCS-related nine-membered ring epoxydiyne which exhibits antitumour activity in human cancers (Figure 7).\(^{60}\) It lacks an amino-sugar residue and was isolated without a carrier protein.\(^{61}\) Its absolute stereochemistry elucidation and the first total synthesis was achieved by Hirama et al.\(^{57}\) In 2006, Myers et al. have reported the second total synthesis of 61.\(^{52}\) Their strategy highlights a transannular cyclisation at C1-C9 to generate the bicyclo-epoxydiyne core. This strategy was also devised for Myers' first total synthesis of the Kedarcidin chromophore.\(^{63}\) As for Hirama's total synthesis of NCS-C,\(^{18}\) the epoxide is introduced after the core generation.

![Figure 7. Structure of N1999-A2.](image)

The synthesis of the key starting 1,5-hexadiyne-3,4-diol derivative 65 is described below (Scheme 11). Z-Selective Wittig reaction from the propargylic ketone 35 and the phosphonium salt 62 followed by selective desilylation give the enediyne 63. Sharpless asymmetric dihydroxylation (SAD)\(^{64,65}\) from 63 leads to diol 64. Protecting group manipulations afford the diastereoisomer 65 in 55% yield.
Scheme 11. Synthesis of 1,5-hexadiyne-3,4-diol via SAD.

The total synthesis of N19999-A2 then starts with a Sonogashira coupling between 65 and the iodo-vinyl stannane 66 followed by further transformations to give 67 (Scheme 12). 67 is then subjected to copper-mediated intramolecular oxidative acetylene coupling affording the substrate 68 for the transannular cyclisation. Treatment of 68 under basic conditions and on 20-25 mg scale affords 69 in moderate yields. Larger scale reactions were less efficient. Selective allylic alcohol deprotection from 69, naphthoate installation via DCC-coupling and protecting group adjustments lead to 70. Epoxide installation from the trans-diol function of 70 affords 71 which was subjected to protecting groups cleavage to give 61.
1.13 Conclusions

The epoxydiyne chromoproteins have been the subject of intense investigations from synthetic, biological and medicinal chemists. Due to their unusual structure and their unstability, they represent a real synthetic challenge. The total synthesis of the NCS-C and N1999-A2 has led to the development of original and highly specific methodologies. The different syntheses reported led to a few milligrams of the natural product being obtained. Owing to the scarcity of *Streptomyces carzinostaticus* in the environment, an improved total synthesis of NCS-C would be very valuable. This requires the development of an original, efficient and concise strategy in order to obtain the natural product on a multi-gram scale and to enable structure/function studies. This would represent a better alternative to fermentation sources.
2 RESULTS AND DISCUSSION

2.1 Retrosynthetic analysis

Our convergent strategy for the synthesis of NCS-C (Scheme 13) involves a key Michael addition of the functionalised cyclopentenone 72 with the epoxydiyne 73 to form the C1-C2 bond. Conjugate addition of an alkynyl group to a cyclic α,β-enone has only been achieved in a few cases with organozinc\textsuperscript{66}, organoaluminium\textsuperscript{67} and rarely with organo-copper reagents\textsuperscript{68}. The conjugate addition of 72 to the epoxydiyne 73 will therefore represent a real synthetic challenge. This should be followed by cyclisation via a cobalt-mediated aldol reaction to form the C8-C9 bond and the bicyclic core.\textsuperscript{48} It was already known that under acidic conditions cobalt-complexed acetylenic aldehydes ionise to a stabilised propargyl cation susceptible to nucleophilic attack.\textsuperscript{69} Furthermore, the complexation of Co\textsubscript{2}CO\textsubscript{6} introduces a C-C≡C bond angle distortion from 180° to 145°. These two factors should release the bicyclic epoxydiyne core strain and ease the cyclisation, the distortion making the propargyl cation at C8 closer to the nucleophilic site at C9. Finally, the cobalt-capped intermediates should be protected from decomposition for the next steps of the synthesis. This strategy requires a regioselective coordination of Co\textsubscript{2}CO\textsubscript{6} to the alkyne C6=C7.
Scheme 13. Retrosynthetic analysis.

The naphthoate 44 should be installed at C11-OH via DCC-mediated esterification.\textsuperscript{51} The synthesis of the naphthoate has been reported five times in the literature\textsuperscript{54, 59, 70} and successfully coupled with various cyclopentenoid species. Diastereoselective reduction of the carbonyl group at C10 would lead to the hydroxyl group necessary for the installation of the amino-sugar 74. The synthesis of 74 has been already reported in the literature and condensed by means of a Schmidt coupling to the NCS-C aglycon\textsuperscript{17}. Dehydration at C8-OH and C12-OH should afford the cobalt-protected NCS-C. It is then envisaged that removal of the dicobalt hexacarbonyl group by mild oxidation in the presence of the apo-NCS will prevent the reactive natural product from decomposition \textit{via} cycloaromatisation and give NCS.

2.2 A-ring synthesis

Building on work carried out by Hoffmann \textit{et al.},\textsuperscript{71} a practical approach has been developed within the Caddick group for the preparation of a highly functionalised cyclopentenone. Hoffmann \textit{et al.} had synthesised the cyclopentenone 77 \textit{via} oxidative
rearrangement of fufuryl alcohol 75 followed by protection and palladium/base-mediated ring contraction of 76 (Scheme 14).

\[ \text{Scheme 14. Hoffmann's synthesis of cyclopentenone.} \]

To be suitable and practical on a large scale, the procedure was greatly optimised within the Caddick group.\textsuperscript{72} We started our studies towards the total synthesis of the NCS-C by carrying out a large scale preparation of the cyclopentenone 82 following the procedure developed in the group with some modifications. Furfuryl alcohol 75 was treated with methanolic bromine which, following quenching with gaseous ammonia, gave rise to the dihydrofuran species 78. We found that it was important to maintain the saturation of the solution with gaseous ammonia for 2 h to obtain 78 in high yield. Acid-catalysed ring expansion followed by acetylation gave the acetoxy-pyranone 79. This could be transformed to tert-buty ether pyranone 80 by substitution of the acetate group under acidic conditions. Finally base-mediated ring contraction (81) and TBS-protection led to the functionalised cyclopentenone 82 as a racemic mixture. The tert-butyl ether removal under Lewis acidic conditions using the original procedure led to the cyclopentenone 83 in only 40% with notable decomposition of the starting material 82. We then decided to carry out the transformation at low temperature controlling the reaction time. The tert-butyl ether was found to be easily removed at -78 °C in 5 min in an improved yield (Scheme 15).

To carry out the total synthesis of the NCS-C, the cyclopentenone was required to be enantiomerically pure. Inspired by Hirama et al., Etheridge within the Caddick group investigated an asymmetric desymmetrisation of the dihydroxylated cyclopentenone 83. The reaction involves a lipase-mediated kinetic resolution in which the lipase Amano AK performs a selective acylation of 83 leaving the required cyclopentenone enantiomer 72 untouched. We carried this out on a large scale, in excellent yield and high enantioreselectivity.

Scheme 16. Lipase-mediated kinetic resolution.
Interestingly, 84 could be recycled in a reduction/oxidation sequence via protecting group manipulation to give back the cyclopentenone 72 or alternatively 84 can be used as a synthon towards the total synthesis of the Kedarcidin chromophore (Scheme 17).

![Scheme 17. Recycling of the undesired cyclopentenone.]

### 2.3 Model study

In order to investigate our own Michael addition/intramolecular aldol sequence, the enediyne model 88 has been synthesised efficiently within the group and on a large-scale.\(^{75}\) Inspired by Myers et al.,\(^{50}\) the enediyne 88 was readily prepared using palladium cross-coupling methodology to incorporate the acetylenic moieties (Scheme 18).

![Scheme 18. Synthesis of an enediyne via Sonogashira coupling.\(^{75}\)]

The conjugate addition/intramolecular aldol sequence was first investigated by Delisser.\(^{75}\) The intermediate 89 has been synthesised via diastereoselective aluminium-mediated Michael addition of the enediyne 88 on the cyclopentenone 83 taking advantage of the free alcohol to guide the addition by aluminium chelation.\(^{67c}\) Protection of the alcohol, regioselective alkyne cobalt-complexation, followed by
acetal cleavage led to the aldol precursor 90. Boron/cobalt-mediated aldolisation\textsuperscript{48} gave rise to 91 in good yield (Scheme 19).

Scheme 19. Conjugate addition/intramolecular aldol strategy.

With this model study proving the viability of the Michael/aldol sequence, efforts in our laboratory have been directed to the key epoxydiyne synthesis to which this sequence will be applied towards the NCS-C.

2.4 Previous work towards the synthesis of enediynes within the Caddick group

Preliminary work focused on the synthesis of enediynes with the correct stereochemistry for the introduction of the epoxide ring using a Sharpless asymmetric epoxidation.\textsuperscript{76,77} A route developed within the Caddick group involved a dehydration strategy leading to enediyne 94. Alcohol 93 was prepared by oxidative cleavage of the D-mannitol derivative 92, addition of (trimethylsilyl)acetylene to the resulting aldehyde, oxidation with PDC and finally nucleophilic addition of propargyl Grignard.\textsuperscript{78} Dehydration of 93 via base-mediated elimination of the mesylate led to
the enediyne 94 in 38% yield with a E:Z ratio of 2:1.\textsuperscript{79} Alternatively, dehydration of 93 and concomitant introduction of the acetal functionality \textit{via} a zinc-mediated acetalisation at high temperature led to the separable enediyynes 95, in poor yield but with good diastereoselectivity (E:Z / 10:1) (Scheme 20).\textsuperscript{79}

![Scheme 20](image)

Scheme 20. Enediyne synthesis \textit{via} dehydration.

Hirama \textit{et al.} have published a new and concise route to epoxydiynes (Scheme 21).\textsuperscript{80} The synthesis involves a magnesium-mediated carboalumination pioneered by Fallis,\textsuperscript{81} to give a key E-enediyne. The intermediate diynediol 96 was prepared from the D-glyceraldehyde acetonide 34. Treatment of 34 with triphenylphosphine, potassium tert-butoxide and iodoform followed by acetonide deprotection led to the iodo-alkyne 96. Copper-mediated coupling of 96 with (triethysilyl)acetylene gave rise to the diynediol 97. Carbometalation with ethynyl Grignard in THF afforded the key E-enediyne 98 exclusively in a good yield. Selective TBS-protection of the primary alcohol, followed by Sharpless epoxidation and protecting group adjustments led to the epoxydiyne 99.
Scheme 21. Hirama’s epoxydiyne synthesis via carbometalation.

This approach towards the synthesis of our key epoxydiyne was attempted within the group preparing substrates including C8 as discussed earlier.\textsuperscript{82} Copper-mediated coupling of the iodo-alkyne 95 was achieved using protected propargyl alcohols affording 100, 101, 102 in yields ranging from 25% to 78%. Unfortunately, the magnesium-mediated metalation on these substrates failed to give the corresponding E-enediyne 103 and only starting material was recovered (Scheme 22).

Scheme 22. Attempted enediyne synthesis via carbometalation strategy.
Other olefination strategies were investigated in the Caddick group. Building from Myers’ methodology to epoxydiynes$^{51}$ (Scheme 5, above), Etheridge examined a fairly conventional potential strategy involving a Horner-Wadsworth-Emmons (HWE) reaction (Scheme 23).$^{82}$ The first approach aimed at synthesising the required E-enediyne using a phosphorus reagent incorporating C8. The phosphonate ester reagent 106 was synthesised from but-2-yn-1,4-diol. Monosilylation followed by bromination led to 105 which was subjected to the Arbuzov conditions to give the phosphonate ester 106 in 59% yield. The propargylketone 35 was made from the D-mannitol derivative 92 via oxidative cleavage, trimethylsilylacetylene addition and oxidation with PDC. 35 were then subjected to 106 under HWE conditions. However, all attempts to isolate the intermediate 107 resulted in decomposition of the starting material. These results were attributed to the instability of the phosphonate perhaps via cumulene formation.


A second olefination approach was examined within the group$^{82}$ and involved a reaction of the propargyl ketone 35 with the commercially available bromomethyltriphenylphosphonium salt. This reaction proceeded in good yield but unfortunately gave exclusively the Z-vinyl bromide 108 (Scheme 24). The stereochemistry was confirmed by nOe studies in which no enhancement between $H5$
and H13 were observed. Despite this we decided to examine a possible isomerisation strategy and hence installed the second acetylenic moiety including C8 via a Sonogashira coupling which led to the isolation of the Z-enediyne 109 in 54% yield. This methodology provides an expeditious access to Z-enediyynes including C8 but failed to give the desired E-enediyne. Photochemical isomerisation of 109 was then attempted under the conditions reported by Trost et al.83 Unfortunately, no isomerisation to generate 110 was observed and the starting material was recovered in good yield.

![Chemical structures and reactions](image)

**Scheme 24.** Attempted enediyne synthesis via Wittig/Sonogashira approach.

In summary, previous work in the Caddick group has resulted in an asymmetric synthesis of the cyclopentenone, which I have optimised for scale up, and the Michael addition/intramolecular aldol sequence has been evaluated successfully on an enediyne model. However, the synthesis of the required epoxydiyne is yet to be realised and represents therefore a significant synthetic challenge towards the total synthesis of the NCS-C.
2.5 Synthetic strategies towards epoxydiynes

2.5.1 First strategy: the allylic alcohol elongation approach

In order to carry out our Michael/aldol strategy to the synthesis of NCS-C, we needed to prepare the appropriate epoxydiyne to include C8. Our first approach considered the preparation of the epoxydiyne 111 from the enediyne 112 via a Sharpless asymmetric epoxidation (SAE) then an oxidation-Wittig olefination/Sharpless asymmetric dihydroxylation (SAD)\textsuperscript{64} sequence to install the diol at C13 and C14 (Scheme 25).

![Scheme 25. Retrosynthetic analysis towards epoxydiyne.]

118 was prepared using palladium chemistry to install the two acetylenic moieties. Stereospecific addition of bromide to ethylpropiolate 113 gave the \textit{cis}-dibromide 86\textsuperscript{30} which could undergo a regioselective Sonogashira coupling to give 87 in good yield. Ester reduction (114), alcohol silylation (115), desilylation (116) and zinc-mediated acetalisation under Dean-Stark conditions led to the functionalised enyne 117. The other alkyne was incorporated \textit{via} a Sonogashira coupling to give the enediyne 118 (Scheme 26).\textsuperscript{75,84}
Scheme 26. Enediyne synthesis via Sonogashira approach.

The allylic alcohol 111 was prepared in high yield by treating the enediyne 118 with TBAF and then subjected to the SAE (Scheme 27).

Scheme 27. Sharpless asymmetric epoxidation.

We first applied the standard conditions reported by Sharpless (Table 1, entry 1). Unfortunately, no epoxydiyne 119 was isolated under these conditions. We then increased the amount of titanium/tartrate catalyst, but no reaction occurred and notable decomposition of the starting material was seen (Entry 2). Warming the temperature to -5 °C led to only 10% conversion to the desired epoxydiyne 119 (Entries 3-4). No reaction occurred using a small amount of catalyst to avoid decomposition of the starting material (Entries 5-7) and the increase of the
temperature to +4 °C led to decomposition of the starting material (Entry 8). Finally, varying the amount of TBHP resulted in no change (Entry 9).

<table>
<thead>
<tr>
<th>Entry</th>
<th>D(-)-DET equiv.</th>
<th>Ti(i-PrO)₄ equiv.</th>
<th>T °C</th>
<th>TBHP 5 equiv.</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.1</td>
<td>1.1</td>
<td>-20 °C</td>
<td>5</td>
<td>No reaction, 112 recovered in 62% yield.</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>2</td>
<td>-20 °C</td>
<td>5</td>
<td>No reaction, 112 recovered in 25% yield.</td>
</tr>
<tr>
<td>3</td>
<td>1.1</td>
<td>1.1</td>
<td>-5 °C</td>
<td>5</td>
<td>10% yield, 112 recovered in 27% yield</td>
</tr>
<tr>
<td>4</td>
<td>1.1</td>
<td>1.1</td>
<td>-5 °C</td>
<td>5*</td>
<td>119 (10% yield), 112 recovered in 30% yield</td>
</tr>
<tr>
<td>5</td>
<td>0.2</td>
<td>0.2</td>
<td>-20 °C</td>
<td>5</td>
<td>No reaction, 112 recovered in 85% yield.</td>
</tr>
<tr>
<td>6</td>
<td>0.2</td>
<td>0.2</td>
<td>-5 °C</td>
<td>5</td>
<td>No reaction, 112 recovered in 75% yield.</td>
</tr>
<tr>
<td>7</td>
<td>0.2</td>
<td>0.2</td>
<td>+4 °C</td>
<td>5</td>
<td>No reaction</td>
</tr>
<tr>
<td>8</td>
<td>1.1</td>
<td>1.1</td>
<td>+4 °C</td>
<td>5</td>
<td>Decomposition</td>
</tr>
<tr>
<td>9</td>
<td>1.1</td>
<td>1.1</td>
<td>-20 °C</td>
<td>10</td>
<td>No reaction, 112 recovered in 58% yield.</td>
</tr>
</tbody>
</table>

*: TBHP prepared in a DCM solution (5.2 M)

Table 1. SAE conditions.

The epoxydiyne 119 was formed in poor yield making this route non-viable for future work. Myers et al. have achieved the epoxidation on similar enediynes⁴⁹,⁵¹ and from this, we proposed that the pendant acetal functionality might coordinate the titanium/tartrate catalyst suppressing its catalytic effect and undergoes decomposition. Facing this disappointing result, we sought an alternative route towards the required epoxydiyne.
2.5.2 *Z*-iodo-alkenlyolate precursor for SAE and acetylenic-group installation

Our second approach towards the key epoxydiyne synth on is based on the elaboration of an iodo-alkenlyolate ester intermediate with the required *Z*-stereochemistry set for the Sharpless asymmetric epoxidation (Scheme 28). 73 should be prepared from the epoxy-alcohol 122 through Corey-Fuchs homologation followed by C8-incorporation and TMS-removal at C2. 122 would be elaborated from 121 via Sonogashira coupling to introduce the TMS-acetylenic unit followed by Sharpless asymmetric epoxidation. 121 should be available from the α,β-acetylenic ester 120 via stereoselective acid-catalysed iodide addition; the stereocentre at C13 deriving from the chiral pool D-mannitol derivative 92.

![Scheme 28. Retrosynthetic analysis toward our key fragment.](image)

Precedent for this strategy came from the work of Bruckner and Hirama. Bruckner *et al.* have reported a synthesis of the enediyne 126, related to our key epoxydiyne 73, from the corresponding Z-enol triflate 124 as key intermediate (Scheme 29). Addition of ethyl lithioacetate to the D-glyceraldehyde 34 and subsequent Dess-Martin oxidation led to the β-oxo ester 123 in 49% overall yield. Treatment of 123 with NaH and the chlorinated Comins reagent led to 124 in 62% yield. The trimethylsilylacetylene could be incorporated on 124 by Cacchi coupling in 82% yield and the aldehyde 125 resulting from a reduction-oxidation manipulation, was
homologated using lithio(trimethylsilyl)diazomethane to give the enediyne 126 in a moderate yield.

Scheme 29. Bruckner's enediyne synthesis via a Z-enol triflate intermediate.

Hirama et al. have reported the synthesis of the epoxydiyne 16, a key fragment of the NCS-C.47 Their strategy involves a Wittig reaction on the propargylic ketone 35 leading to the E-alkenylolate intermediate 127 with the correct stereochemistry for the Sharpless epoxidation. A reduction/oxidation sequence gave the aldehyde to which a Corey-Fuchs reaction was carried out to give the intermediate vinyl dibromide. Protecting group manipulations, followed by treatment with n-BuLi gave the E-enediyne 128. Subsequent SAE followed by protecting group adjustments gave the trans-epoxydiyne 16 (Scheme 30).

Both reported strategies suggested the feasibility of our approach. Our strategy would shorten the route of Hirama and circumvent the use of the non-commercially available chlorinated Comins' reagent. The major synthetic challenge relies upon the stereospecific synthesis of the acetonide-Z-iodo-alkenyloate 120. Piers et al. have reported a facile method to prepare substituted (Z)-iodo-alkenyloate 130 by stereoselective addition of iodide on the alkyl α,β-acetylenic ester 129 using sodium iodide and acetic acid at high temperature in yields ranging from 35% to 98% (Scheme 31).

Scheme 31. Z-iodo-alkenyloate ester synthesis via stereocontrolled halide addition.

To test the feasibility of this method, we decided to synthesise the appropriate acetylenic ester 132. This was prepared in a four-step sequence in an overall yield of 60% from the d-mannitol derivative 92. d-Glyceraldehyde 34 was prepared from oxidative cleavage of 92 with sodium periodate in DCM/NaHCO₃(aq) and was
converted to the ester 131 via the Corey-Fuchs procedure. Accordingly, the aldehyde 34 was treated with carbon tetrabromide and triphenylphosphine in DCM to afford the 1,1-dibromoalkene 131. Subsequent treatment of 131 with 2 equiv. of n-BuLi in THF at -78 °C followed by quenching with methyl chloroformate led to required ester 120 (Scheme 32). This sequence could be carried out on a 100 g scale.

Scheme 32. Synthesis of the acetylenic ester via Corey-Fuchs protocol.

Initially, Dr H. Britton also working in this area in the Caddick group, established good conditions for the conversion of 120 to the Z-iodo alkenyloate 121. Employing 1.5 equiv. of sodium iodide and 1.6 equiv. of acetic acid in acetonitrile at reflux gave the required product 121 in 95% yield revealing the stability of the acetonide group under the reaction conditions (Scheme 33). We carried out nOe experiments, which caused enhancement between $H_5$ and $H_{13}$, demonstrated the stereochemistry of the double bond and that no isomerisation of the double bond occurred under these conditions.
Scheme 33. Z-iodo-alkenyloate ester synthesis via stereocontrolled halide additon.

Our approach then involves the incorporation of the first acetylenic moiety to the Z-iodo-alkenyloate 121 via a Sonogashira coupling.\cite{91} Using the conditions reported by Fiandanese et al. with structurally similar compounds,\cite{92} (trimethylsilyl)acetylene was coupled to 121 with tetrakis(triphenylphosphine)palladium (0.05 equiv), copper iodide (0.1 equiv.) and triethylamine (3 equiv.) in acetonitrile to give the acetylenic substituted E-alkenyloate 127 in 99% yield. The expected configuration of 127 was confirmed by comparison of the NMR reported by both Hirama\cite{47} and Bruckner\cite{86} by nOe experiments showing that no isomerisation of the double bond occurred under the reaction conditions (Scheme 34).

Scheme 34. Eneynye synthesis via Sonogashira coupling.

In order to investigate the SAE reaction, the acetylenic E-alkenyloate 127 was reduced with DIBAL in ether at low temperature affording the allylic alcohol 132 in high yield (Scheme 35).
The \textit{E}-allylic alcohol 135 was subjected to SAE. We decided first to use the original conditions reported by Sharpless \textit{et al.} (Scheme 36).\textsuperscript{76} Accordingly, 132 was treated with a stoichiometric amount of chiral titanium IV isopropoxide/\textit{d}-(\textit{S})-diethyltartrate catalyst system, 5 equiv. of \textit{tert}-butyl hydroperoxide (TBHP solution in DCM) and activated powdered molecular sieves in DCM at -20 °C for 96 h. The desired epoxy-alcohol 122 could not be isolated and complex mixtures of unidentified compounds were observed by TLC (Table 2, entry 1). Increasing the amount of catalyst led to decomposition (Entry 2). We then tested using a small amount of catalyst to avoid decomposition, warming the temperature or varying the amount of TBHP, but we were unable to isolate the epoxy-alcohol 122 (Entries 3-6).

\textbf{Scheme 36.} Sharpless asymmetric epoxidation (SAE).
<table>
<thead>
<tr>
<th>Entry</th>
<th>D-(-)-DET (equiv.)</th>
<th>Ti(i-PrO)₄ (equiv.)</th>
<th>TBHP (equiv.)</th>
<th>T °C</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.1</td>
<td>1.1</td>
<td>5</td>
<td>-20°C</td>
<td>No reaction, small amount of unidentified compounds</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>2</td>
<td>5</td>
<td>-20°C</td>
<td>No reaction, significant decomposition (96 h)</td>
</tr>
<tr>
<td>3</td>
<td>0.2</td>
<td>0.2</td>
<td>5</td>
<td>-20°C</td>
<td>No reaction</td>
</tr>
<tr>
<td>4</td>
<td>0.2</td>
<td>0.2</td>
<td>5</td>
<td>-5°C</td>
<td>No reaction</td>
</tr>
<tr>
<td>5</td>
<td>0.2</td>
<td>0.2</td>
<td>8</td>
<td>-5°C</td>
<td>No reaction</td>
</tr>
<tr>
<td>6</td>
<td>0.2</td>
<td>0.2</td>
<td>5*</td>
<td>-5°C</td>
<td>No reaction</td>
</tr>
</tbody>
</table>

*: TBHP in a decane solution (5 M)

Table 2. SAE conditions.

We postulated that the two oxygen atoms of the C13/C14-diol system might coordinate the catalyst making it inactive or that alternatively there might be a steric clash between the TMS group and the chiral catalyst preventing its efficient complexation to alcohol 132 to guide the oxidation. Finally, we also considered that the alkoxide/catalyst complex may be causing the cleavage of the TMS protecting group to initiate decomposition. In view of these considerations, we hoped that the desilylated allylic alcohol 133 may be a more viable substrate for the SAE. 133 was prepared in one step with TBAF in THF at 0 °C in 93% yield (Scheme 37).

![Scheme 37. TMS-deprotection.](image)

The allylic alcohol 133 was subjected to SAE (Scheme 38). Epoxidation of 133 with the standard Sharpless conditions at -20 °C led to the epoxy-alcohol 134 in 45%
yield (Table 3, entry 1). Unidentified by-products were still detected by TLC plate suggesting that the epoxy-alcohol was quite unstable under these conditions likely due to epoxide opening. We then carried out an optimisation study on this reaction. Increasing the amount of catalyst led to a lower yield likely due to decomposition of 134 (Entry 2). We then chose to decrease the amount of catalyst to avoid decomposition from conditions reported by Sharpless et al. and 134 was obtained in a slightly improved yield (Entry 3). Increasing the amount of TBHP resulted in no change (Entry 4). Treatment of 133 (0.2 M) with 0.2 equiv. of the titanium-tartrate catalyst and TBHP (in a DCM solution) at -6 °C gave the epoxy-alcohols 134 and 135 in 71% yield in a 10:1 ratio respectively (Entry 5). Warming the temperature led to a better yield but to an increase in 135. However, the diastereoisomeric purity was still greatly in favour of 134. At -20 °C, the diastereoisomer 135 was present in insignificant quantity (Entry 3). We decided then to increase the concentration of substrate to 0.5 M to speed up the reaction and we found the conditions for an efficient conversion to 134 in 72h (Entry 6). The type of TBHP used is also very important for the reaction to succeed. Under the same conditions with a commercially available solution of TBHP in decane, the reaction proceeded in low yield (Entry 7). The reduced amount of catalyst used has greatly simplified the isolation procedures and solved the problem of decomposition. nOe experiments confirmed the trans stereochemistry of 134 with enhancement between H5 and H13 confirming that no isomerisation of the double bond occurred. We assumed that the oxygen atom of the epoxide possessed the same stereochemistry as that of the NCS-C from the reliable Sharpless rules.77
Scheme 38. Sharpless asymmetric epoxidation.

<table>
<thead>
<tr>
<th>Entry</th>
<th>D(-)-DET (equiv.)</th>
<th>Ti(i-PrO)₄ (equiv.)</th>
<th>TBHP (equiv)</th>
<th>T</th>
<th>Concentration of 133 (mol/L)</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.1</td>
<td>1.1</td>
<td>5</td>
<td>-20 °C</td>
<td>0.2</td>
<td>45%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>134</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>2</td>
<td>5</td>
<td>-20 °C</td>
<td>0.2</td>
<td>13%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>134</td>
</tr>
<tr>
<td>3</td>
<td>0.2</td>
<td>0.2</td>
<td>5</td>
<td>-20 °C</td>
<td>0.2</td>
<td>58%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>134</td>
</tr>
<tr>
<td>4</td>
<td>0.2</td>
<td>0.2</td>
<td>8</td>
<td>-20 °C</td>
<td>0.2</td>
<td>48%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>134</td>
</tr>
<tr>
<td>5</td>
<td>0.2</td>
<td>0.2</td>
<td>5</td>
<td>-6 °C</td>
<td>0.2</td>
<td>71%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>134 : 135</td>
</tr>
<tr>
<td>6</td>
<td>0.2</td>
<td>0.2</td>
<td>5</td>
<td>-6 °C</td>
<td>0.5</td>
<td>81%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>134 : 135</td>
</tr>
<tr>
<td>7</td>
<td>0.2</td>
<td>0.2</td>
<td>5*</td>
<td>-6 °C</td>
<td>0.5</td>
<td>32%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>134</td>
</tr>
</tbody>
</table>

*: TBHP in a decane solution

Table 3. Optimisation of the SAE.

Having established a good procedure to synthesise the epoxy-alcohol 134, we turned our efforts to the conversion of the alcohol into the second alkyne. Unfortunately, the
fact that the SAE proceeded only with the TMS-removed substrate 133, meant that the homologation reaction would lead to an unprotected epoxydiyne making the C8-incorporation rather delicate. However, we carried on the synthesis to study the feasibility of the homologation (Scheme 39). Oxidation of 134 with Dess-Martin periodinane \(^\text{94}\) led to the desired epoxy-aldehyde 136. NMR of the crude mixture revealed the presence of the characteristic proton at 9.47 ppm and total disappearance of starting material. 136 appeared to be highly silica-sensitive preventing its purification. We then anticipated that the one carbon homologation to the alkyne should be generated through a Corey-Fuchs protocol \(\text{via}\) the dibromoalkene intermediate. However, all attempts to isolate the dibromo-olefin 137 using conditions originally reported, \(^\text{85}\) consistently failed and led to decomposition of the sensitive aldehyde 136 (Table 4, entry 1). Lowering the amount of the active reagent of the CBr\(_4\)/PPh\(_3\) mixture as well as the temperature gave the same results (Entries 2-4). As mentioned by McKelvie et al., the CBr\(_4\)/PPh\(_3\) mixture would lead to the \textit{in situ} formation of the dibromotriphenylphosphine which was discovered to be a strong electrophile as well as a brominating agent. \(^\text{95}\) For instance, the byproduct is known to initiate epoxide-ring opening, \(^\text{96}\) silyl ether cleavage \(^\text{97}\) and TBHP deprotection. \(^\text{98}\) It may therefore represent the source of the degradation of 136.

\[ \text{Scheme 39. Attempted homologation } \text{via}\  \text{Corey-Fuchs approach.} \]
<table>
<thead>
<tr>
<th>Entry</th>
<th>PPh₃ (equiv.)</th>
<th>CBr₄ (equiv.)</th>
<th>T</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4</td>
<td>2</td>
<td>0 °C</td>
<td>No reaction/Decomposition of 136</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>2</td>
<td>0 °C</td>
<td>No reaction/Decomposition of 136</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>2</td>
<td>-78 °C</td>
<td>No reaction/Decomposition of 136</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td>2</td>
<td>-78 °C</td>
<td>No reaction/Decomposition of 136</td>
</tr>
</tbody>
</table>

Table 4. Investigations studies towards the dibromoalkeke.

A modified procedure of the Corey-Fuchs protocol applied to sensitive aldehydes has been widely reported. This employs Et₃N which likely makes the reaction conditions less vigorous by suppressing the side effects of Br₂PPh₃. We decided to submit 136 to these conditions (Scheme 40). We found that addition of a preformed solution of the epoxyaldehyde 136 with Et₃N to the CBr₄/PPh₃ mixture at -78 °C led to the expected epoxy-dibromoalkene 137 in moderate yield (Table 5, entry 1). 137 was isolated in poorer yield by increasing the temperature (Entry 2) or the amount of Et₃N (Entry 3).

![Scheme 40](image)

Scheme 40. Homologation of epoxyaldehyde via milder Corey-Fuchs conditions.
<table>
<thead>
<tr>
<th>Entry</th>
<th>PPh₃ (equiv.)</th>
<th>CBr₄ (equiv.)</th>
<th>Et₃N (equiv.)</th>
<th>T</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>2</td>
<td>1.5</td>
<td>-78 °C</td>
<td>53%</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>2</td>
<td>1.5</td>
<td>0 °C</td>
<td>15%</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>2</td>
<td>6</td>
<td>-78 °C</td>
<td>32%</td>
</tr>
</tbody>
</table>

Table 5. Optimisation of Corey-Fuchs procedure.

We then turned our efforts to the conversion of 137 to the epoxydiyne 138 (Scheme 41). Dibromoalkene intermediates are usually treated with n-BuLi at low temperature in THF to give the alkynyl lithium which can be quenched by H₂O or MeOH to give the terminal alkyne. Alternatively, the alkynyl lithium can be trapped by various electrophiles, in this case to incorporate C8. The formation of the alkyne from the dibromoalkene 137 turned out to be very difficult. The literature procedure employing n-BuLi⁸⁵ failed to give the epoxydiyne 138. We therefore looked for a much milder base to carry out the transformation. Employing NaHMDS,⁹⁹c KHMDS or DBU at low temperature failed to give the bromoalkyne 138 and led to decomposition of the starting material. Finally TBAF proved to be the best reagent for the conversion but still led to a complex mixture, which appeared to include the epoxydiynes 138 and 139. Despite our best efforts to optimise the reaction, we were unable to isolate 138 and 139 pure and in good yield. Treatment of the crude mixture with 1.0 equiv. of n-BuLi followed by trapping with TESCl afforded a complex mixture which was thought to include the monosilylated and disilylated epoxydiynes 16, 140 and 141 from NMR analysis of the crude mixture.
Scheme 41. Preparation of epoxydiynes.

The Shioiri methodology\textsuperscript{100} was tested by carrying out the reaction using Bruckner’s\textsuperscript{86} conditions. We were unable to isolate the epoxydiyne 139 and complex mixture of unknown compounds were obtained instead (Scheme 42).

Scheme 42. Attempted epoxydiyne syntheis via Shioiri approach.

We also attempted to use other methods to obtain the epoxydiynes. Our first alternative method was to generate the alkyne by employing phosphonate reagents. We prepared the Seyferth-Gilbert reagent,\textsuperscript{101} dimethyl diazomethylphosphonate (DAMP), from a recently reported procedure (Scheme 43).\textsuperscript{102} Dimethyl methylphosphonate 145 was trifluoroacetylated to give the intermediate 143. 143 was then treated with 4-acetamidobenzenesulfonyl azide yielding 144.
Scheme 43. Synthesis of the Seyferth-Gilbert reagent.

The reaction of the phosphonate 144 with the epoxialdehyde 136 in the presence of t-BuOK failed to give the required epoxydiyne 139 and led to total decomposition of the starting material. We proposed that the anion of the dimethyl diazomethylphosphonate may induce epoxide ring opening.

Scheme 44. Attempted epoxydiyne synthesis using Seyferth-Gilbert reagent.

Our next method was to employ dimethyl 1-diazo-2-oxopropylphosphonate, known as Ohira’s reagent, in the presence of basic methanol. 146 was obtained in a single step by reacting the commercially available dimethyl-2-oxopropylphosphonate 145 with tosyl azide in good yield (Scheme 45).

Scheme 45. Synthesis of the Ohira’s reagent.
The epoxyaldehyde 136 was then reacted with 146 in potassium carbonate and methanol (Scheme 46). After stirring for several hours at rt, the epoxidyne 139 could not be isolated and decomposition of 136 was observed. Carrying out the reaction at low temperature led to the same results. We suspected that methanol could induce epoxide opening. t-Butanol was then chosen as solvent to avoid nucleophilic addition but the same result was observed. Phosphonate reagents appeared to behave as strong nucleophiles, leading to the decomposition of the sensitive epoxyaldehyde 136.

Scheme 46. Attempted epoxidyne synthesis using Ohira’s reagent.

We also attempted an alternative Horner-Wadsworth-Emmons olefination approach. Our strategy aimed at synthesising the required epoxidyne 148 from 136 and the α-iodo-phosphonate 147 incorporating C8 followed by 1,2-halogeno-elimination (Scheme 47).

Scheme 47. HWE/elimination strategy.

The phosphonate 150 was prepared in good yield using the commercially available 2-bromo-1,1-dimethoxyethane and trimethylphosphite at 120 °C. Unfortunately, α-
iodination of 150 using N-iodosuccinimide and NaH failed to give the required phosphonate 147 (Scheme 48). This was likely due to β-elimination of methoxide under basic conditions.

Scheme 48. Attempted phosphonate synthesis.

We decided then to carry out the HWE olefination of 136 by using the known trimethyl α-iodo-phosphonoacetate 152.105 152 was prepared by α-iodination of the commercially available trimethyl phosphonoacetate 151 with NaH and N-iodosuccinimide. It is proposed that olefination of the epoxyaldehyde 136 led to the epoxy-vinyliodide 153 however it was found to be highly silica-sensitive, preventing purification. However NMR of the crude mixture revealed the presence of the characteristic vinylic proton at 6.7 ppm of 153 and total disappearance of starting material (Scheme 49).

Scheme 49. Attempted vinyl iodide synthesis via HWE olefination.
We then concentrated our effort towards the 6,7-elimination of the crude vinyl iodide 153 (Scheme 50). Attempts to isolate 154 were carried out from conditions reported in the literature\textsuperscript{106} and failed to give the epoxydiyne 154. Varying the solvent and the base led to decomposition of the starting material (Table 6).

![Chemical Structures](image)

**Scheme 50.** Attempted epoxydiyne synthesis via 6,7-elimination.

<table>
<thead>
<tr>
<th>entry</th>
<th>solvent</th>
<th>base</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DME</td>
<td>NaH</td>
<td>Decomposition</td>
</tr>
<tr>
<td>2</td>
<td>THF</td>
<td>NaH</td>
<td>Decomposition</td>
</tr>
<tr>
<td>3</td>
<td>THF</td>
<td>DBU</td>
<td>Decomposition</td>
</tr>
<tr>
<td>4</td>
<td>THF/DMSO</td>
<td>t-BuOK</td>
<td>Decomposition</td>
</tr>
<tr>
<td>5</td>
<td>THF</td>
<td>TBAF</td>
<td>Decomposition</td>
</tr>
</tbody>
</table>

**Table 6.** Attempted epoxydiyne synthesis via 6,7-elimination.

Despite our efforts directed towards the synthesis of epoxydiynes via this route, we were unable to obtain the desired products so it was decided to seek an alternative route.

### 2.5.3 General method to epoxydiynes and a key fragment of the NCS-C

Our initial attempts towards epoxydiynes had unfortunately failed to yield the desired compound. Despite considerable work we had been unable to incorporate the C8 carbon on the epoxydiyne fragment essential for our conjugate addition/intramolecular aldol strategy to NCS. We turned then to a potentially more
rapid and general alternative to unsymmetrical epoxydiynes.\textsuperscript{107} Our convergent strategy towards our key epoxydiyne disconnects at C4-C5. It involves a Darzens-type condensation\textsuperscript{108} of a propargylic halide with the corresponding propargylic ketone (Scheme 51). This has the potential to deliver a highly practical and convergent methodology to the desired fragment and circumvents a Sharpless asymmetric epoxidation that requires the synthesis of the corresponding enediyne with the correct stereochemistry and protecting group adjustments.

Scheme 51. Retrosynthetic analysis towards the key epoxydiyne using a Darzens-type approach.

In using this approach we face three synthetic challenges, namely the diastereoselectivity of the condensation, the nucleophilicity and the stability of the propargylic halide. Normant \textit{et al.} have recently reported that an allenyl zinc bromide 157, made from the corresponding propargylic chloride, can be added to various aldehydes and selected ketones to give chlorohydrins which can be readily cyclised to propargylic epoxides in good overall yield.\textsuperscript{109} The organo-zinc reagent was chosen because of their good regioselectivity in nucleophilic addition to aldehydes and their improved thermal stability by comparison with other organo-metal counterparts. The allenyl zinc reagent was prepared at low temperature from the starting propargylic chloride 156 using 2 equiv. of zinc bromide followed by dropwise addition of 2 equiv.
of LDA. The reactivity of this new, nucleophilic reagent was tested by Normant et al. on a variety of aldehydes and ketones to give the corresponding chlorohydrins in good yields (Scheme 52).

![Scheme 52](image)

**Scheme 52.** Normant’s preparation of the allenyl zinc bromide and diastereoselective synthesis of chlorohydrins.\(^{109}\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>R’</th>
<th>Yield (%)</th>
<th>anti/syn ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(n)-Bu</td>
<td>H</td>
<td>81</td>
<td>85/15</td>
</tr>
<tr>
<td>2</td>
<td>(i)-Pr</td>
<td>H</td>
<td>75</td>
<td>95/5</td>
</tr>
<tr>
<td>3</td>
<td>(t)-Bu</td>
<td>H</td>
<td>82</td>
<td>98/2</td>
</tr>
<tr>
<td>4</td>
<td>CH(_3)-CH=CH(_2)</td>
<td>H</td>
<td>82</td>
<td>84/16</td>
</tr>
<tr>
<td>5</td>
<td>Ph-CH=CH(_2)</td>
<td>H</td>
<td>75</td>
<td>80/20</td>
</tr>
<tr>
<td>6</td>
<td>CH(_2)=CH</td>
<td>CH(_3)</td>
<td>91</td>
<td>50/50</td>
</tr>
<tr>
<td>7</td>
<td>Ph</td>
<td>H</td>
<td>85</td>
<td>64/36</td>
</tr>
<tr>
<td>8</td>
<td>4-MeO-Ph</td>
<td>H</td>
<td>66</td>
<td>63/37</td>
</tr>
<tr>
<td>9</td>
<td>3,4,5-MeO-Ph</td>
<td>H</td>
<td>85</td>
<td>71/29</td>
</tr>
<tr>
<td>10</td>
<td>4-NO(_2)-Ph</td>
<td>H</td>
<td>74</td>
<td>47/53</td>
</tr>
<tr>
<td>11</td>
<td>2,4-NO(_2)-Ph</td>
<td>H</td>
<td>74</td>
<td>35/65</td>
</tr>
</tbody>
</table>

**Table 7.** Influence of the substituents on the diastereoselectivity of the reaction.\(^{109}\)

In the case of aliphatic aldehydes, the diastereoselectivity of the condensation is in favour of the anti-isomers (anti/syn: 85/15 to 98/2) (Table 7, entries 1-3).
Furthermore, they found that the bulk of R greatly influences the diastereoisomeric ratio in favour of the anti-adducts. Slightly less diastereocouplon is observed in the case of alkenyl-aldehydes (anti:syn / 84:16 to 80:20) (Entries 4-5). No diastereocouplon was observed in the case of the ketone used (anti:syn / 50:50) (Entry 6). A remarkable drop in diastereoselectivity was observed in the case of the aromatic aldehydes even leading to inversion of stereocontrol when electron-withdrawing substituents such as NO₂ were present on the aromatic ring (anti:syn / 64:36 to 35:65) (Entries 7-11).

The corresponding chlorohydrins were converted into propargylic epoxides in 35% to 99% yield. The preparation of desilylated propargylic epoxides 162 and 163 was achieved by protodesilylation with KF in wet DMF followed by ring closure in 10% aqueous NaOH. Alternatively, treatment of the chlorohydrins with DBU leads to TMS-protected propargylic epoxides 164 and 165. (Scheme 53).

Scheme 53. Diastereospecific cyclisation of chlorohydrins into propargylic epoxides.¹⁰⁹

Chlorohydrins cyclised in a diastereospecific manner; the diastereoisomeric anti/syn ratio of chlorohydrins predicting respectively the diastereoisomeric trans/cis ratio of the resultant epoxides (Table 8).
<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>R’</th>
<th>Method</th>
<th>Yield (%)</th>
<th>trans/cis ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>i-Pr</td>
<td>H</td>
<td>A</td>
<td>35</td>
<td>95/5</td>
</tr>
<tr>
<td>3</td>
<td>t-Bu</td>
<td>H</td>
<td>B</td>
<td>97</td>
<td>98/2</td>
</tr>
<tr>
<td>4</td>
<td>CH₂=CH₂</td>
<td>H</td>
<td>B</td>
<td>93</td>
<td>84/16</td>
</tr>
<tr>
<td>5</td>
<td>Ph-CH=CH₂</td>
<td>H</td>
<td>A</td>
<td>90</td>
<td>80/20</td>
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<tr>
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<td></td>
<td></td>
<td>B</td>
<td>98</td>
<td>80/20</td>
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<td>6</td>
<td>Ph</td>
<td>H</td>
<td>A</td>
<td>95</td>
<td>64/36</td>
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<td>B</td>
<td>99</td>
<td>64/36</td>
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<tr>
<td>7</td>
<td>4-MeO-Ph</td>
<td>H</td>
<td>A</td>
<td>97</td>
<td>63/37</td>
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<td></td>
<td></td>
<td></td>
<td>B</td>
<td>94</td>
<td>63/37</td>
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<tr>
<td>11</td>
<td>-(CH₂)₅-</td>
<td></td>
<td>A</td>
<td>74</td>
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</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>B</td>
<td>96</td>
<td>Not given</td>
</tr>
<tr>
<td>12</td>
<td>CH₂=CH</td>
<td>CH₃</td>
<td>B</td>
<td>98</td>
<td>50/50</td>
</tr>
</tbody>
</table>

**Table 8.** Conversion of chlorohydrins to propargylic epoxides.\(^{109}\)

To explain the formation of the major (+/-) anti-chlorohydrins, the authors invoked a favoured chelate transition state in which the allenyl moiety and the C=O bond are eclipsed and in which the chlorine atom and the substituents R of the carbonyl adopt an anti position. The syn chlorohydrins come from the disfavoured transition state in which the R substituents and the halogen atom are in a syn position and thus involve a steric clash (Figure 8). Subsequent cyclisation of the anti and syn isomers then led to the trans and cis epoxydiynes respectively.

**Figure 8.** Proposed transition state model to explain the diastereoselectivity.
Inspired by their work, preliminary studies were performed to test the feasibility of this approach toward epoxdiynes and to investigate the stereoselectivity (Scheme 54). Trimethylsilylation of the commercially available propargyl chloride with $n$-BuLi gave the propargylic chloride 156. Treatment of 156 with 2 equiv. of zinc bromide followed by dropwise addition of 2 equiv. of LDA at low temperature was assumed to afford the allenyl zinc bromide reagent 157. Promisingly the addition of 2-octynal to this mixture gave the 2 inseparable chlorohydrin diastereoisomers 168 and 169. Isolation and purification of the chlorohydrins could not be achieved due to their instability. Immediate desilylation of the crude chlorohydrins using KF in DMF followed by cyclisation with DBU gave rise to the inseparable diastereoisomeric epoxydiynes 170 and 171 in a cis:trans / 3:5 ratio and in 42 % overall yield. Extensive purification allowed small amounts of each epoxide to be obtained for full characterisation. The trans isomer was thus confirmed to be the major product due to its smaller coupling constant. Attempts at cyclisation with potassium carbonate in methanol or H$_2$O/NaOH failed to give the epoxydiynes and the TMS-deprotected chlorohydrins were obtained. Furthermore, TMS-protected epoxydiynes could not be obtained by treatment with DBU; a complex mixture of unknown products being generated.
Scheme 54. Preparation of the allenyl zinc bromide and synthesis of epoxydiynes.

The stereochemical outcome is in agreement with the transition state model described above with the major stereoisomer being generated from a transition state minimising the steric interactions between the alkyne and the chlorine atom. The diastereospecific cyclisation via an S_N2 mechanism then leads to the transfer of stereochemical integrity to the epoxydiyne products (Figure 9).
Figure 9. Chelate-type transition state for diastereoselectivity.

According to this transition state model, we postulated that propargylic ketones with a bulky α-group that is sterically more demanding than the alkyne, should preferentially lead to trans epoxydiynes. Furthermore, the stereochemical outcome of the addition of acetylides to erythulose derivatives structurally similar to our synthon 35 has been investigated previously (Figure 10). Stereoselective addition of ethynyl Grignard to ketone derivatives gave syn and anti-adducts in good yield with a high level of diastereoselectivity depending on the conditions used. An α-chelation transition state involving the α-oxygen of the acetonide and a chelating agent such as Ti(i-PrO)₄ can be used to explain the observation that the major adduct is syn rationalised by nucleophilic addition to the Re side of the ketone. Alternatively, in the absence of the Ti(i-PrO)₄ the major anti adduct is obtained by addition to the Si face of the ketone. This is explained by involving a six-membered chelate involving the β-oxygen of the acetonide with the magnesium or through a Felkin-Ahn transition state.
Building from these studies, we hoped that the chiral center which will be \((R-C13)\) at the \(\alpha\)-position of the ketone 35 would influence the addition of the allenyl zinc reagent to the \(Si\) face of the ketone to favour the formation of the alcohol with the required \(R\)-stereochemistry at \(C4\). This can be rationalized by proceeding \textit{via} a \(\beta\)-chelation transition state involving the zinc or non-chelation Felkin-Ahn transition state (Figure 11).

To test this, the propargylic ketone 35 was initially prepared from the commercially available chiral D-mannitol derivative 92 (Scheme 55). Oxidative cleavage of 91 with sodium periodate followed by addition of lithium (trimethylsilyl)acetylide to D-glyceraldehyde acetonide 34 led to diastereoisomeric propargylic alcohols 172 as a
mixture in a 1.2:1 ratio and in 75% yield over 2 steps. Oxidation with pyridinium dichromate or Dess-Martin periodinane gave the required ketone 35 in 84% or 95% yield respectively. Dess-Martin periodinane is easier to handle and far less toxic than PDC but more expensive for scale-up purpose.

Scheme 55. Synthesis of the chiral propargylic ketone.

A colleague, Dr Baker then carried out the addition of the allenyl zinc reagent 157 to 35. From four possible stereoisomers obtainable in this reaction, one major chlorohydrin 173 was observed from NMR analysis of the crude mixture. Subsequent treatment with KF led to the removal of both silyl groups and cyclisation, to give a mixture of diastereoisomeric epoxydiynes of which only 139 was cleanly isolable in a moderate yield (Scheme 56).

Scheme 56. Epoxidyne synthesis via stereoselective condensation.
The stereochemistry of this product was confirmed by comparison with the work of Hirama. Baker followed the synthesis of Hirama to give the epoxydiyne 16, and subsequent removal of the TES group yielded the epoxydiyne 139, which had identical spectroscopic properties. Thus the stereochemical outcome of this two-step sequence matched the desired stereochemistry of the epoxydiyne moiety of NCS-C (Scheme 57).

Scheme 57. Confirmation of the stereochemistry.

Encouraged by this result, we extended this protocol to unsymmetric trisubstituted epoxydiynes. To date, only Myers and Hirama have reported the synthesis of such epoxydiynes and used 39 and 16 respectively as valuable intermediates for their studies towards the total synthesis of NCS-C (Figure 12).

Figure 12. Stereochemical structure of Myers and Hirama epoxydiynes.
We therefore attempted to synthesise 39 and 16 to provide a new and general access to epoxydiynes previously reported in the literature. The appropriate TES and TBS-protected propargyl chlorides 174 and 175 were made using the same procedure as for the preparation of 156. Subsequent treatment with zinc bromide and LDA afforded the reactive organozinc reagents 176 and 177 (Scheme 58).

![Scheme 58. Preparation of the allenyl zinc bromide reagents.](image)

The addition of the corresponding allenyl zinc compounds 176 and 177 respectively to the propargylic ketone gave one major chlorohydrin 178 from NMR analysis of the crude mixture. In each case again the isolation and characterisation of the chlorohydrins could not be achieved due to their instability. Subsequent treatment of this mixture with potassium carbonate in methanol at low temperature led to selective TMS-removal and concomitant ring closure affording a mixture of epoxydiynes of which the major product 16 and 39 respectively, was cleanly isolable in good yield (Scheme 59). The other diastereoisomers were present in complex mixtures thus preventing the determination of reliable diastereoisomeric ratios. The stereochemistry of the isolated epoxydiynes were the same as those reported by Hirama and Myers. In the latter case the completion of the synthesis of NCS-C with 39 unambiguously confirmed the stereochemistry. Furthermore comparison of the \( \alpha_D \) of 39 and 16 with the literature suggested that no racemisation of ketone 35 occurred under the basic conditions of the addition.
Scheme 59. Diastereoselective synthesis of key unsymmetric epoxydiynes.

As mentioned above, our general strategy toward the NCS-C has been to include the C8 carbon in the epoxydiyne synthon. To do this using the allenyl zinc methodology required an appropriately substituted propargylic chloride. 155 was prepared from the commercially available propargyloxytrimethysilane 179. Functionalisation using diethylphenyl orthoformate with ethyl magnesium bromide to include the C8 followed by immediate desilylation afforded the propargyl acetal 180 in good yield after distillation.\textsuperscript{112} Mesylation immediately followed by substitution with TBAC gave the functionalised propargylic chloride 155 in good yield which was of sufficient purity after work-up (Scheme 60).

Scheme 60. Synthesis of the required propargyl chloride.

The application of the allenyl zinc method to such a fragment appears very challenging. In the presence of a strong base 155 could isomerise into cumulene 182 with ethoxide elimination. Alternatively, deprotonation at C8 would lead to the undesired allenyl zinc 183. The latter could lead to another cumulene 184 with loss of chloride. Due to the products obtained, it is thought that 181 is formed in the presence of zinc bromide/LDA \textit{via} deprotonation occurring in the \(\alpha\)-position to the chlorine at C5, likely due to steric bulk considerations. No cumulene degradation was observed (Figure 13).
The allenyl zinc reagent 181 condensed to the propargylic ketone 35 in a diastereoselective manner affording two inseparable chlorohydrins 185 and 186 in an anti:syn / 10:1 ratio after purification. In that case the two chlorohydrins could be isolated in only 60% yield after purification. Traces of the two other diastereoisomers were also just visible by NMR but only in negligible quantities. Subsequent treatment of this mixture with KF in DMF led to the separable desilylated epoxydiynes 73 and 187 in a trans: cis / 10:1 ratio from which our key synthon 73 was isolated in 66% over two steps. The stereochemistry of the epoxydiynes was confirmed by NMR experiments allowing the stereochemistry of the chlorohydrins to be deduced.
Scheme 61. Diastereoselective synthesis of a key epoxydiyne intermediate toward Neocarzinostatin.

It is worth noting that no cyclisation of chlorohydrins resulting from the addition to propargylic aldehydes (e.g. 188) proceeded in the presence of KF/DMF/H₂O or K₂CO₃/MeOH. In contrast chlorohydrins resulting from the addition to the propargylic ketone readily cyclised in these two conditions. This difference in reactivity can be explained by the Thorpe-Ingold effect. In the case of the more substituted chlorohydrin 185, the α angle is smaller than the α angle for the chlorohydrin 188. The acetonide group repels and forces the hydroxyl group closer to the C₄-C₅ bond. Therefore the cyclisation demands less entropy loss to cyclise (Figure 14).
Figure 14. Illustration of the Thorpe-Ingold effect.

To try to further improve the diastereoselectivity of the transformation, the cyclohexylidene ketal was used in place of the isopropylidene group. A bulkier protected group might influence the stereochemical addition to the adjacent carbonyl group of our key propargylic ketone 35. The cyclohexyl ketal was chosen as Britton found that the addition of propargyl Grignard with 191 gave a better diastereoselectivity 4:1 in favour of the required R stereochemistry at the C4 carbon compared to 1:1 with 35 (Scheme 62).90

Scheme 62. Influence of the cyclohexylidene ketal group on the diastereoselectivity.
Thus 191 was made from the commercially available d-mannitol derivative 194 (Scheme 63). The same sequence was applied as in the case of 35. In this sequence, the oxidation with PDC proved difficult, and the propargylic ketone 191 was isolated in 22% overall yield. Eventually, 191 was obtained in 15 h and in 55% overall yield by employing 2.5 equivalents of Dess-Martin periodinane.

Scheme 63. Synthesis of the required propargylic ketone.

The chlorohydrin formation (197 and 198) proceeded with good diastereoselectivity (anti/syn: 5/1) and subsequent cyclisation with concomitant desilylation afforded diastereoisomeric epoxydiynes 199 and 200 (trans:cis / 5:1) from which the required product was isolated in 53% overall yield (Scheme 64). Surprisingly, a bulkier group at the α-position to the ketone does not seem to influence the stereocontrol of the reaction.
Scheme 64. Diastereoselective synthesis of the key epoxydiyne.

2.5.4 Conclusions

The development of a general strategy for a synthesis of epoxydiynes has proven to be extremely difficult due to the formation of unstable intermediates which could not be processed to the fully elaborated epoxydiyne. After considerable investigations, we finally found that the addition of allenyl zinc bromide to propargylic ketones and aldehydes provides an expeditious entry to stereochemically pure epoxydiynes. For our particular project the ability to introduce the C8 portion required for NCS-C is particularly useful. It is noteworthy that the present protocol provides a very simple synthetic route to other functionalised epoxydiynes which have previously found use in the synthesis of NC-C. Epoxydiynes can be prepared in order to test our Michael/aldol sequence.
2.6 Michael Addition Studies

The Michael addition reaction of organometallic species to α-β-unsaturated carbonyls represents a powerful method for carbon-carbon bond formation. Organocopper reagents are the most widely used for Michael addition of alkyl and alkenyl groups to cyclic or acyclic α-β enones.\textsuperscript{114} Alkynylcopper reagents have rarely been employed\textsuperscript{68-115} as copper does not readily transfer the alkynyl group to the conjugated system due to the strength of the alkynyl-Cu(I) bond.\textsuperscript{116} Pappo et al. found that 1,4-addition of organoaluminium acetylenic reagents 201 to cyclic enone 202 gave 203 with chirality transferred from the free hydroxyl group.\textsuperscript{67c} The hydroxyl group chelates the organoaluminium species and then the alkynyl group is transferred in a diastereoselective manner from the aluminium in a 1,4 fashion via a possible five-membered ring transition state intermediate (Figure 15).

![Figure 15. Diastereoselective Michael addition.](image)

Inspired by Pappo’s work,\textsuperscript{67c} Caddick et al. have optimised the Michael addition of the enediyne 88 with the enone 83 to give 89 (Scheme 65). The organoaluminium reagent was prepared by treating 88 with n-BuLi followed by transmetalation using Et\textsubscript{2}AlCl. The method has also been extended to the related-NCS-C enediyne 204 and the brominated enone 205 to give 206 in a moderate yield as a 1:1 mixture of diastereoisomers.\textsuperscript{79}
Scheme 65. Michael addition.\textsuperscript{79}

We then decided to test the diastereoselective aluminium-catalysed Michael addition under the conditions reported by Caddick \textit{et al.}\textsuperscript{75} This reaction was initially investigated using the epoxidyne 16 and the cyclopentenone 72 (Scheme 66). The alkynylation reagent was prepared from the starting epoxidyne 16 using 1.0 equiv. of \textit{n}-BuLi at -78 °C followed by addition of 1.3 equiv. of \textit{Et}_2\text{AlCl}. The reaction was then stirred for 1 h at rt. Addition of the cyclopentenone 72 to the alkynylation reagent at -40 °C failed to give the cycloadduct 207 (Table 9, entry 1). Carrying out the reaction in \textit{Et}_2\text{O} (entry 2) or toluene (entry 3) also proved to be unsuccessful. The same result was observed employing \textit{Me}_2\text{AlCl} (Entry 4), LDA (Entries 5-6) or increasing the temperature to 0 °C or rt (Entries 7-10).
Scheme 66. Attempted Michael addition.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagent</th>
<th>Base</th>
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</tr>
</thead>
<tbody>
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<td>1</td>
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<td>n-Buli</td>
<td>THF</td>
<td>-40 °C</td>
<td>No reaction</td>
</tr>
<tr>
<td>2</td>
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<td>n-Buli</td>
<td>Et₂O</td>
<td>-40 °C</td>
<td>No reaction</td>
</tr>
<tr>
<td>3</td>
<td>Et₂AlCl</td>
<td>n-Buli</td>
<td>Toluene</td>
<td>-40 °C</td>
<td>No reaction</td>
</tr>
<tr>
<td>4</td>
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<td>THF</td>
<td>-40 °C</td>
<td>No reaction</td>
</tr>
<tr>
<td>5</td>
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<td>THF</td>
<td>-20 °C</td>
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</tr>
<tr>
<td>6</td>
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<td>LDA</td>
<td>THF</td>
<td>-20 °C</td>
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</tr>
<tr>
<td>7</td>
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<td>THF</td>
<td>0 °C</td>
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</tr>
<tr>
<td>8</td>
<td>Me₂AlCl</td>
<td>n-Buli</td>
<td>THF</td>
<td>0 °C</td>
<td>No reaction</td>
</tr>
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<td>9</td>
<td>Et₂AlCl</td>
<td>n-Buli</td>
<td>THF</td>
<td>rt</td>
<td>No reaction</td>
</tr>
<tr>
<td>10</td>
<td>Me₂AlCl</td>
<td>n-Buli</td>
<td>THF</td>
<td>rt</td>
<td>No reaction</td>
</tr>
</tbody>
</table>

Table 9. Attempted Michael addition.

We postulated that the C4 position of 72 was not activated enough towards nucleophiles. We then envisaged activating C4 through bromination of 72 at C3 under basic conditions (Scheme 67).

Scheme 67. Cyclopentenone bromination under basic conditions.
However, when the brominated cyclopentenone 208 was used under the same conditions as for 72, no reaction was observed and both starting materials were recovered quantitatively (Table 10, entries 1-10).

**Scheme 68.** Attempted Michael addition.

<table>
<thead>
<tr>
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<th>Base</th>
<th>Solvent</th>
<th>T</th>
<th>Results</th>
</tr>
</thead>
<tbody>
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<td>THF</td>
<td>-40 °C</td>
<td>No reaction</td>
</tr>
<tr>
<td>2</td>
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<td>n-Buli</td>
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<td>-40 °C</td>
<td>No reaction</td>
</tr>
<tr>
<td>3</td>
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<td>Toluene</td>
<td>-40 °C</td>
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</tr>
<tr>
<td>4</td>
<td>Me&lt;sub&gt;2&lt;/sub&gt;AlCl</td>
<td>n-Buli</td>
<td>THF</td>
<td>-40 °C</td>
<td>No reaction</td>
</tr>
<tr>
<td>5</td>
<td>Et&lt;sub&gt;2&lt;/sub&gt;AlCl</td>
<td>n-Buli</td>
<td>THF</td>
<td>0 °C</td>
<td>No reaction</td>
</tr>
<tr>
<td>6</td>
<td>Me&lt;sub&gt;2&lt;/sub&gt;AlCl</td>
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<td>THF</td>
<td>0 °C</td>
<td>No reaction</td>
</tr>
<tr>
<td>7</td>
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<td>n-Buli</td>
<td>THF</td>
<td>rt</td>
<td>No reaction</td>
</tr>
<tr>
<td>8</td>
<td>Me&lt;sub&gt;2&lt;/sub&gt;AlCl</td>
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<td>No reaction</td>
</tr>
<tr>
<td>9</td>
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<td>LDA</td>
<td>THF</td>
<td>-20 °C</td>
<td>No reaction</td>
</tr>
<tr>
<td>10</td>
<td>Me&lt;sub&gt;2&lt;/sub&gt;AlCl</td>
<td>LDA</td>
<td>THF</td>
<td>-20 °C</td>
<td>No reaction</td>
</tr>
</tbody>
</table>

**Table 10.** Optimisation studies.

We decided to vary the protecting group of 16 at C13-C14 as we thought the acetonide represented a problem for the reaction to succeed. We chose to protect the diol moiety through silylation. By following the synthesis of Hirama to give the epoxydiyne 16, Baker within the Caddick group made the intermediate 209 which we thought would represent a valuable substrate for the silylation. Thus, silylation of 209 under basic conditions led to 210 in high yield (Scheme 69).
Scheme 69. Silylation of epoxydiyne.

210 was then submitted to the Michael addition conditions with the cyclopentenones 208 and 72 respectively (Scheme 70). However, no reaction was observed using the same conditions previously described (See table 9 and 10) and both starting materials were recovered quantitatively (Table 11, entry 1-10). We assumed that the alkynyl aluminium species was not nucleophilic enough towards the cyclopentenones. We then decided to increase the basicity by using Et3N and some molecular sieves to trap water. We were pleased to observe the Michael adduct 212 as a single diastereoisomer by using these conditions. 211 Was not detected and 72 was recovered quantitatively.

Scheme 70. Attempted Michael addition.
<table>
<thead>
<tr>
<th>Entry&lt;sup&gt;a&lt;/sup&gt;</th>
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<th>Base</th>
<th>Solvent</th>
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</tr>
</thead>
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<td>THF</td>
<td>-40 °C</td>
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</tr>
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<td>2</td>
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<td>-40 °C</td>
<td>No reaction</td>
</tr>
<tr>
<td>3</td>
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<td>Toluene</td>
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<td>THF</td>
<td>-40 °C</td>
<td>No reaction</td>
</tr>
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<td>n-Buli</td>
<td>THF</td>
<td>0 °C</td>
<td>No reaction</td>
</tr>
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<td>THF</td>
<td>0 °C</td>
<td>No reaction</td>
</tr>
<tr>
<td>7</td>
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<td>n-Buli</td>
<td>THF</td>
<td>Rt</td>
<td>No reaction</td>
</tr>
<tr>
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<td>THF</td>
<td>Rt</td>
<td>No reaction</td>
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<tr>
<td>9</td>
<td>Et&lt;sub&gt;2&lt;/sub&gt;AlCl</td>
<td>LDA</td>
<td>THF</td>
<td>-20 °C</td>
<td>No reaction</td>
</tr>
<tr>
<td>10</td>
<td>Me&lt;sub&gt;2&lt;/sub&gt;AlCl</td>
<td>LDA</td>
<td>THF</td>
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</tr>
<tr>
<td>11&lt;sup&gt;+&lt;/sup&gt;</td>
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<td>n-Buli</td>
<td>THF</td>
<td>-20 °C</td>
<td>10% 212, no reaction using 72</td>
</tr>
<tr>
<td>12&lt;sup&gt;+&lt;/sup&gt;</td>
<td>Et&lt;sub&gt;2&lt;/sub&gt;AlCl</td>
<td>n-Buli</td>
<td>THF</td>
<td>-20 °C</td>
<td>No reaction</td>
</tr>
</tbody>
</table>

<sup>a</sup>: Cyclopentenone 72 and 208 was used for each entry.

Table 11. Optimisation studies.

We decided to screen the conditions for the Michael addition using our key intermediate 73 and cyclopentenones 72 and 208 (Scheme 71). Unfortunately, conjugate addition under the conditions previously described proved unsuccessful (Table 12, entries 1-12). We found that 73 decomposed using n-BuLi/Et<sub>2</sub>AlCl or n-BuLi/Me<sub>2</sub>AlCl (Entries 1-8). The use of the LDA/Et<sub>2</sub>AlCl system partially solved the problem of decomposition. We decided then to increase the amount of 73 to 4 equiv. but no product was observed (Entries 13-14). Adding a Lewis acid such as BF<sub>3</sub>.Et<sub>2</sub>O during the reaction (Entry 15) failed to give 213 and 214 respectively, even by increasing the temperature (Entries 16-17). Corey et al. have reported that complete reaction of trimethysilylacetylene with Me<sub>2</sub>AlCl takes 5h at 10 °C. Unfortunately, we found that the alkynylaluminium decomposed at room temperature under these conditions (Entry 18).
Scheme 71. Attempted Michael addition.
<table>
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<tr>
<th>Entry</th>
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<td>0 °C</td>
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</tr>
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<td>rt</td>
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<tr>
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<td>LDA</td>
<td>THF</td>
<td>-20 °C</td>
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<td>Et₂AlCl</td>
<td>LDA</td>
<td>THF</td>
<td>rt</td>
<td>No reaction</td>
</tr>
<tr>
<td>18ᵈ</td>
<td>Me₂AlCl</td>
<td>LDA</td>
<td>THF</td>
<td>rt</td>
<td>No reaction</td>
</tr>
</tbody>
</table>

ᵃ: Cyclopentenones 72 or 210 were used for each entry.ᵇ: 4 equiv. of the epoxydiyne 73 was used.ᶜ: Addition of BF₃·Et₂O.ᵈ: Organometallic reagent stirred for 5h at 10°C.

Table 12. Attempted Michael addition.

We assumed that the alkynylaluminium might not be generated efficiently or that the oxygen atoms of the diol C13/C14 might coordinate the organoaluminium reagent making it inactive towards the conjugate addition.

Facing these disappointing results, we turned to alternative methods for conjugate addition. Schwartz et al. have reported the conjugate addition of alkynyl groups to cyclic α,β-enones using organoaluminium reagents in the presence of Ni(I), generated
in situ by a reduction of Ni(acac)$_2$ with DIBAL.$^{67a,b}$ We decided to apply this method to the cyclopentenone 215 (Scheme 72). 215 was prepared by reacting 72 with pivaloyl chloride under basic conditions in good yield. 215 was then reacted with epoxydiyne 73 under Schwartz’ conditions. Unfortunately, 216 was not detected and only 215 was recovered quantitatively. 73 was found to decompose under these conditions.

![Scheme 72. Attempted conjugate addition.](image)

Another method has been reported using alkynylzinc reagents.$^{66}$ This requires the use of an activator such as TBSOTf. The organozinc 217 is generated by deprotonation of 216 using $n$-BuLi followed by transmetalation with ZnBr$_2$. Condensation of 218 to cyclopentenone 219 lead to 220 in 72% (Scheme 73).$^{66}$ Within the group, the conjugate addition has been achieved with the cyclopentenone 83 and phenylacetylene 218 to give 221 as a mixture of diastereoisomers in a 4:1 ratio in 56% yield (Scheme 71).$^{79}$
Scheme 73. Zinc-mediated Michael addition.

We then decided to apply the same conditions to the addition of 73 to 83. 73 was treated with n-BuLi followed by ZnBr₂. Enone 83 was then added followed by TBSOTf at -40 °C. No reaction was observed however and both starting materials were recovered (73: 26%, 83: 52%). We also applied the same conditions using the cyclopentenone 219 but without any success (Scheme 74).
Nilsson et al. have achieved the conjugate addition of alkynylcopper reagents to cyclic enones using TMSI as promoter. Conjugate addition of 224 to cyclopentenone 225 using the conditions reported has been achieved by Dr Baker (Scheme 75). 224 was treated with n-BuLi followed by CuI at low temperature to give 225. TMSI was then added and the mixture was reacted with 219 to give 226 in high yield after hydrolysis.

Scheme 74. Attempted zinc-mediated Michael addition.

Scheme 75. Copper-mediated Michael addition.
We then applied these conditions to 73 and the enones 219 and 82 (Scheme 76). We decided to apply a basic work-up as reported by Nilsson et al.\textsuperscript{68} in order to obtain the TMS enol-ether product as we thought the hydrolysis of 227 or 228 via desilylation would decompose under aqueous acidic conditions (HCl 3M).\textsuperscript{68} No product was detected however and 73 could not be recovered in either case.

![Chemical structures](image)

**Scheme 76.** Attempted copper-mediated Michael addition.

Lastly we decided to retry the aluminium-catalysed Michael addition with a epoxydiyne more stable towards acidic conditions. The epoxydiyne 199 protected as its cyclohexyldiene ketal at C13-C14-diol was chosen. The conjugate addition was then submitted to the original conditions reported by Caddick et al. (Scheme 79).\textsuperscript{75} Unfortunately no product was observed carrying out the reaction at -40 °C but both starting materials were recovered quantitatively solving the stability problem when making the organoaluminium reagent. Unfortunately, we were unable to carry out any further investigations on this reaction due to time constraints.
The first priority of future work towards the NCS-C would be to test the aluminium-mediated conjugate addition with 199. 199 may require a longer exposure to Et₂AlCl or Me₂AlCl to be generated efficiently. Once this goal is achieved, the cobalt-mediated aldol reaction would be tested.

2.7 Future work and alternative strategies

2.7.1 Intramolecular Michael addition

Having experienced problems with the intermolecular Michael addition, another approach to generating the macrocycle of NCS-C would be to carry out the conjugate addition intramolecularly. The C8-C9 bond would first be formed through a Baylis-Hillman reaction followed by a Michael addition leading to the core of NCS-C (Figure 16).
In order to carry out the conjugate addition intramolecularly, another alternative would be to introduce a linker-bearing epoxydiyne 233 on the free alcohol of 234. The resulting substrate 235 would be processed through a Michael addition to give 236. The linker would be cleaved under conditions that do not degrade the product and the aldol reaction would be tested affording 237 (Figure 17).

Figure 16. Baylis-Hillman/Michael sequence.

Figure 17. Intramolecular Michael/aldol sequence.
2.7.2 Other strategies

Our synths would be coupled using other approaches to give the core of NCS-C. The first sequence involves a Sonogashira coupling between 238 and 239 at C1-C2 to give 240. This would be followed by a macrocyclisation through a McMurry coupling affording 241 (Figure 18).

![Diagram showing chemical structures](image)

Figure 18. Sonogashira/McMurry coupling.

The second sequence requires the synthesis of the synthon 242. 242 would be coupled to the cyclopentenone 239 via a Sonogashira coupling followed by phosphorane preparation to give the Wittig precursor 243. 244 would then be generated by mean of a Wittig olefination (Figure 19).
2.7.3 Model study towards the Kedarcidin chromophore

Kedarcidin chromophore is another antitumour antibiotic whose structure is related to NCS-C.\textsuperscript{63} In the proposed strategy, it is anticipated to test the useful application of the allenyl zinc reaction to form the C8-C9 bond (Figure 20). Inspired by Hirama et al.\textsuperscript{18} conditions, Sonogashira coupling of 245 with 246 would lead to the adduct 247. 247 would then react with 155 in a Darzens-type reaction to give 248. Finally, the C4-C5 double bond would be generated by a Barbier-Grignard reaction followed by elimination to afford the core structure 249 of the Kedarcidin chromophore.
**Figure 20.** Model study towards the kedarcidin chromophore.
3 CONCLUSIONS

The development of a general and new strategy towards epoxydiynes proved to be extremely difficult. Our early strategies were built from the work of Myers, Hirama and Bruckner and turned to be rather long and linear. They led to the generation of unstable intermediates which could not be processed to the fully elaborated epoxydiyne 73. After considerable investigation studies, a concise and convergent approach to epoxydiynes was discovered and applied efficiently on a multi-gram scale. This involves a diastereoselective addition of an allenyl zinc bromide to propargylic ketone/aldehyde followed by epoxide formation. From this method, known epoxydiynes have been successfully synthesised with the correct stereochemistry in good overall yield. Our sequence required only five steps from the D-mannitol derivative compared to Myers (10) and Hirama (9). The allenyl zinc protocol allowed the diastereoselective synthesis of our fully elaborated synthon 73. This enabled us to release C2 and incorporate C8, key sites of our Michael/aldol strategy. Michael addition did not prove successful with our key epoxydiyne partly due to stability problem. However, the epoxydiyne 199 prove to be stable in the aluminium-catalysed conjugate addition. The next priority of the project should be to test this synthon for Michael addition studies. In their total synthesis of the NCS-C, Myers and Hirama have showed that the choice of specific protecting groups is critical for the success of a reaction. Owing to the flexibility of our new method, epoxydiynes with different protecting group can now be readily available enabling us to screen them for Michael addition studies or to pioneer alternative convergent strategies towards the core structure of the NCS-C. Studies are underway to complete the total synthesis of the NCS-C.
4 EXPERIMENTAL

General procedures:
Melting points were obtained using a Gallenkamp variable heater. Optical rotations were measured on a PolaAr 2000 polarimeter. Infrared spectra were recorded on a SHIMADZU FT-IR 8700 spectrometer. Data were presented as frequency of absorption (cm\(^{-1}\)). Proton and carbon NMR were measured on Bruker AMX300 spectrometer, or a Bruker AMX400 spectrometer or a Bruker AVANCE500 spectrometer. Chemical shifts were expressed in parts per million (δ) and are referenced to the residual solvent peak (CHCl\(_3\), 7.26 and C\(_6\)D\(_2\)H, 7.15). The following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet and br, broad. Coupling constants are recorded in Hertz. \(^{13}\)C NMR chemical shift were referenced to resonances of the NMR solvent. Low and high resolution mass spectra were obtained from the mass spectroscopy service at Swansea. Flash chromatography was carried out on silica gel (32-70μm). Thin layer chromatography was performed on aluminium plates pre-coated with Merck silica gel 60 F\(_{254}\) and was visualised by exposure to UV and/or exposure to potassium permanganate or anisaldehyde followed by heating. Dimethyl (diazomethyl)phosphonate was visualised by exposure to iodine. All reactions were performed in flame-dried round bottom flasks and under positive pressure of argon unless otherwise noted. Commercial reagents and solvents were used as received with some exceptions. THF, Et\(_2\)O, CH\(_3\)CN and DCM were distilled through alumina column from an anhydrous engineering apparatus. Methanol was distilled from magnesium turnings and iodine. DMF was distilled from calcium hydride under reduced pressure. Hexamethyldisilazane, diisopropylamine, triethylamine, n-propylamine, diisopropylethylamine, dichloroethane were distilled from calcium hydride at 760 torr. Lithium hexamethyldisilazide (1M in THF/hexanes) and lithium diisopropylamine (1M in THF/hexanes) were freshly prepared by the addition of n-butyllithium (freshly titrated) respectively to a solution of hexamethyldisilazide and diisopropylamine in THF. The molarity of n-BuLi (Acros) was determined by titration using dry [(1S)-endo]-(−)-Borneol and fluorene as indicator. ZnBr\(_2\) 99.999% was purchased from Aldrich. ZnBr\(_2\) (98%) from Aldrich was oven-dried prior to use. Furfuryl alcohol was distilled under reduced pressure from Na\(_2\)CO\(_3\) and stored over molecular sieves 4Å. Molecular sieves 4Å was flame-
activated under reduced pressure at $10^{-3}$ Mbar. Ti (IV) isopropoxide was purchased from Fluka and distilled under reduced pressure at $10^{-3}$ Mbar and stored in a drybox. D(-)-diethyl tartrate was distilled under reduced pressure at $10^{-3}$ Mbar and stored under argon. Anhydrous tert-butyl hydroperoxide (TBHP) was prepared as described: 2 L of aqueous 70% TBHP and 2 L of DCM were shaken twice in a separating funnel. The organic phase was transferred to a 5 L round bottom flask equipped with a condenser and few boiling chips. The mixture was gently refluxed using a heating mantle for 5 days. Water and DCM were distilled out and periodically DCM was added to maintain the volume constant in the flask (ca. 2.5 L). The solution was transferred to high density polyethylene bottle and stored over 250 g of activated molecular sieves 4Å at 4 °C. **CAUTION: EXPLOSIVE; heating must be done in a hazard laboratory and behind a blast shield.** The molarity of TBHP was determined by iodometric titration. Tetrakis(triphenylphosphine)palladium(0) purchased from Strem Chemicals, Inc. and Lipase AK “Amano” 20 purchased from Amano Enzyme Inc. were both stored at -20 °C.
2-Hydroxymethyl-2,5-dimethoxy-3,4-dihydrofuran 78\textsuperscript{72b}

![Chemical Structure](image)

A solution of bromine (136.9 g, 860 mmol) in methanol (239 mL) was slowly added to a stirred solution of furfuryl alcohol (70.4 g, 718 mmol) in a mixture of dry Et\textsubscript{2}O (239 mL) and methanol (239 mL) at -40 °C. Stirring was then continued for a further 2 hours at -40 °C. The resulting light yellow solution was saturated with gaseous ammonia at -70 °C to pH 8 and allowed to warm to ambient temperature. The resulting yellow suspension was filtered, removing ammonium bromide and concentrated \textit{in vacuo}. Further filtration removed the white solid formed upon concentration of the yellow oil. The oil was diluted in benzene (500 mL) and filtered through neutral alumina. Evaporation of the solvent yielded 78 (102.6 g, 91%) as a yellow oil which was seen to be of sufficient purity for use in further stages.

\textit{v}max (cm\textsuperscript{-1}) 3473, 2988, 2837, 1632;

\textsuperscript{1}H (300MHz, CDCl\textsubscript{3}) \textit{δ} \textsubscript{H} 6.04 (d, 1H, J 4.7, CH\textsubscript{alkene}), 5.93 (dd, 1H, J 4.7, 0.9, CH\textsubscript{alkene}), 5.48 (d, 1H, J 0.9, CH\textsubscript{OME}), 3.69-3.52 (m, 2H, CH\textsubscript{2}OH), 3.38 (s, 3H, CH\textsubscript{3}), 3.09 (s, 3H, CH\textsubscript{3}), 1.95 (br s, 1H, OH);

\textsuperscript{13}C (75MHz, CDCl\textsubscript{3}) \textit{δ} \textsubscript{C} 132.2 (CH), 131.3 (CH), 112.9 (CH), 107.3 (CH), 66.6 (CH\textsubscript{3}), 56.2 (CH\textsubscript{3}), 50.4 (CH\textsubscript{2}).
To 2-hydroxymethyl-2,5-dimethoxy-3,4-dihydrofuran 78 (71.4 g, 0.72 mol) in THF (700 mL) and H₂O (25 mL) cooled to 0 °C was added triflic acid (16.6 g, 0.11 mol) producing a dark colouration. The reaction mixture was stirred at 0 °C for 3 h, after which time acetic anhydride (292 g, 2.86 mol) and sodium acetate (235 g, 2.86 mol) were added. The reaction was allowed to warm to room temperature and stirred for 18 h, after which time the resulting orange solution was filtered under vacuum to remove any residual solid. The reaction was quenched by addition of a saturated aqueous solution of NaHCO₃ (500 mL) and additional solid NaHCO₃ (30 g) until effervescence ceased. The mixture was extracted in Et₂O (2 x 1 L), dried over magnesium sulfate, filtered and concentrated in vacuo (cold bath) to yield an orange oil. Flash column chromatography eluting with EtOAc (15%)/PE gave the desired product 79 (77.4 g, 69%) as a yellow oil.

\[ \text{vmax (cm}^{-1}\text{)} \quad 2979, 1707, 1700, 1630, 1264, 998; \]
\[ ^1\text{H} (300 \text{ MHz, CDCl}_3) \delta \text{H} 6.95 \text{ (dd, } 1\text{H, } J 11.1, 3.6, \text{ CH}_\text{alkene}), 6.47 \text{ (d, } 1\text{H, } J 11.1, \text{ CH}_\text{alkene}), 6.32 \text{ (d, } 1\text{H, } J 3.6, \text{ CHOAc}) 4.51 \text{ (d, } 1\text{H, } J 17.4, \text{ CH}_2), 4.23 \text{ (d, } 1\text{H, } J 17.4, \text{ CH}_2), 2.15 \text{ (s, } 3\text{H, CH}_3); \]
\[ ^{13}\text{C} (75 \text{ MHz, CDCl}_3) \delta \text{C} 193.8 \text{ (C=O), 169.9 (C=O), 142.7 (CH), 129.2 (CH), 87.0 (CH), 67.8 (CH}_2), 21.3 (CH}_3). \]
6\textsuperscript{-}Butoxy-2,3-dihydro-6H-pyrano-3-one 80\textsuperscript{72b}

A 1 M solution of tin (IV) chloride in DCM (6 mL, 6 mmol) was slowly added to a stirred solution of 6-acetoxy-2,3-dihydro-6H-pyrano-3-one 79 (17.6 g, 113 mmol) in dichloroethane (10 mL) and tert-butanol (53 mL, 550 mol). Stirring was continued at ambient temperature for 5 h, at which point the reaction was quenched with a saturated aqueous solution of NaHCO\textsubscript{3} (150 mL). The resulting mixture was extracted with ethyl acetate (500 mL), washed with a saturated aqueous solution of NaHCO\textsubscript{3} (50 mL) and H\textsubscript{2}O (40 mL), dried over magnesium sulfate, filtered and concentrated \textit{in vacuo}. Flash column chromatography eluting with EtOAc (10%)/PE afforded the title compound 80 (17.1 g, 89%) as a colourless liquid.

\begin{align*}
\text{vmax (cm}^{-1}\text{)} & \quad 3056, 2979, 1707, 1630, 1392, 1266, 998; \\
^{1}\text{H (300 MHz, CDCl\textsubscript{3})} & \quad \delta_{H} 6.64 (dd, 1H, J 10.2, 3.4, CH\textsubscript{alkene}), 5.95 (d, 1H, J 10.2, CH\textsubscript{alkene}), 5.33 (d, 1H, J 3.4, CHOR-butyl), 4.39 (d, 1H, J 16.9, CH\textsubscript{2}), 3.91 (d, 1H, J 16.9, CH\textsubscript{2}), 1.17 (s, 9H, C(CH\textsubscript{3})\textsubscript{3}); \\
^{13}\text{C (75 MHz, CDCl\textsubscript{3})} & \quad \delta_{C} 195.9 (C=O), 146.6 (CH), 127.6 (CH), 88.3 (CH), 74.7 (C), 66.5 (CH\textsubscript{2}), 28.9 (3 x CH\textsubscript{3}).
\end{align*}
trans-[4-(1,1-Dimethylethoxy)-5-(hydroxy)]-2-cyclopenten-1-one \textsuperscript{84}

![Chemical structure](image)

A stirred solution of pyranone \textbf{80} (42 g, 0.25 mol) in DMF (700 mL) and Et\textsubscript{3}N (16 mL, 1.20 mol) was heated at 80 °C for 24 h. The black reaction mixture was allowed to cool to room temperature and concentrated \textit{in vacuo}. Flash column chromatography eluting with Et\textsubscript{2}O (30%)/PE gave the title compound \textbf{81} (32.8 g, 78%) as a white solid.

\textit{vmax (cm
\textsuperscript{-1})}: 3430, 2979, 1719, 1615, 1393, 1266, 922;

\textit{\textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3})}: \delta_{\text{H}} 7.28 (dd, 1H, J 6.1, 1.8, CH\textsubscript{alkene}), 6.18 (d, 1H, J 6.1, CH\textsubscript{alkene}), 4.56-4.53 (m, 1H, CH/OH), 4.03 (d, 1H, J 2.2, CHO-t-butyl), 3.42 (br s, 1H, OH), 1.25 (s, 9H, C(CH\textsubscript{3})\textsubscript{3});

\textit{\textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3})}: \delta_{\text{C}} 205.5 (C=O), 161.5 (CH), 131.3 (CH), 80.7 (CH), 76.4 (CH), 75.1 (C), 28.2 (3 x CH\textsubscript{3}).
**trans-[4-(1,1-Dimethylethoxy)-5-[[1,1dimethylethyl]dimethylsilyl]oxy]-2-cyclopenten-1-one 82**

![Structural diagram](image)

(+/-)

To the alcohol **81** (10.4 g, 61.2 mmol) stirring in DCM (240 mL) at 0 °C was added TBSCl (13.85 g, 92.0 mmol) followed by portionwise addition of imidazole (6.20 g, 92.0 mmol) after 10 minutes. The mixture was stirred for 2 h, after which time it was quenched with a saturated aqueous solution of NH₄Cl (50 mL) and extracted with DCM (2 x 100 mL). The organics were washed with brine (50 mL), dried over magnesium sulfate, filtered and concentrated *in vacuo*. Flash column chromatography eluting with Et₂O (2%)/PE afforded **82** (17.0 g, 97%) a colourless oil.

\[ \text{vmax (cm}^{-1}) \text{: 2931, 2887, 2858, 1729, 1619, 1587, 1473;} \]

\[ ^1H \text{ (300 MHz, CDCl}_3 \text{) \delta_H : 7.19 (dd, 1H, J 6.3, 1.6, CH}_\text{alkene}, 6.07 (d, 1H, J 6.3, CH}_\text{alkene}, 4.5 (d, 1H, J 1.2, CHOTBS), 4.07 (d, 1H, J 2.9, CH}_\text{tBu}, 1.24 (s, 9H, C(CH}_3)_3, 0.88 (s, 9H, SiC(CH}_3)_3, 0.14 (s, 3H, CH}_3Si, 0.09 (s, 3H, CH}_3Si); \]

\[ ^13C \text{ (75 MHz, CDCl}_3 \text{) \delta_c : 203.3 (C=O), 160.0 (CH), 132.3 (CH), 81.7(CH), 77.6 (CH), 75.3 (C), 28.8 (3 \times CH}_3, 26.2 (3 \times CH}_3, 18.8 (C), -3.8 (CH}_3, -4.7 (CH}_3); \]

HRMS (M+H)\(^+\) calcd. for \( \text{C}_{13}\text{H}_{29}\text{O}_2\text{Si} \) 285.1886, found 285.1886.
trans-[5-[[1,1-Dimethylethyl]dimethylsilyl]oxy]-4-hydroxy]-2-cyclopenten-1-one 83

\[
\text{\begin{center}
\begin{tikzpicture}
\node (a) at (0,0) {\text{OTBS}};
\node (b) at (1,0) {\text{OH}};
\end{tikzpicture}
\end{center}
\] (+/-)

To a stirring solution of cyclopentenone 82 (17.0 g, 59 mmol) in DCM (170 mL) at -78 °C, was added a 1 M solution of TiCl₄ (66 mL, 66 mmol) over 5 min. The reaction was stirred for a further 5 min. The reaction mixture was quenched with a saturated aqueous solution of NaHCO₃ (50 mL), extracted with DCM (3 x 150 mL), washed with brine (50 mL), dried over magnesium sulfate, filtered and concentrated in vacuo. Flash column chromatography eluting with EtOAc (20%)/PE afforded 83 (11.6 g, 85%) as a white crystalline solid.

vmax (cm⁻¹) 3443, 2985, 2927, 2855, 1741, 1593, 1470, 1361, 1283, 1260, 1141, 1117, 1063, 1038, 871, 839, 774, 725;

¹H (300MHz, CDCl₃) δH 7.18 (dd, 1H, J 6.3, 1.9, CHalkene), 6.04 (dd, 1H, J 6.3, 1.2, CHalkene), 4.60-4.56 (m, 1H, CHOTBS), 3.96 (d, 1H, J 2.7, CHO), 2.16-2.14 (br. s, 1H, OH), 0.78 (s, 9H, C(CH₃)₃), 0.04 (s, 3H, SiCH₃), 0.00 (s, 3H, SiCH₃);

¹³C (75MHz, CDCl₃) δC 203.0 (C=O), 158.9 (CH), 143.0 (CH), 82.7 (CH), 78.0 (CH), 26.2 (3 x CH₃), 18.8 (C), -4.1 (CH₃), -4.7 (CH₃);

HRMS (M+H)⁺ calcd. for C₁₁H₂₁O₂Si 229.1260, found 229.1260.
(4S,5R)-4-Hydroxy-5'-butyldimethylsilyloxy-cyclopenten-1-one 72 and (4R,5S)-4-acetoxy-5'-butyldimethylsilyloxy-cyclopenten-1-one 84

![Chemical Structures](image-url)

To 83 (5 g, 21.9 mmol) in benzene (20 mL), was added lipase Amano AK (3.57 g) followed by vinyl acetate (40 mL). The reaction was stirred at 34 °C for 15 h then filtered under reduced pressure and concentrated in vacuo. Flash column chromatography eluting with EtOAc (20%)/PE resulted in 72 (2.5 g, 50%) as a white solid and 84 (2.9 g, 49%) as a colourless oil.

72:
\[ \alpha_D^{22} +118 \text{ (c 1.14 in CHCl}_3\text{)}; \]
\[ \nu_{\text{max}} \text{ (cm}^{-1}) \text{ 3443, 2985, 1741}; \]
\[ ^1H \text{ (300MHz, CDCl}_3\text{) } \delta_H 7.18 \text{ (dd, 1H, J 6.3, 1.9, CH}_\text{alkene}\text{), 6.04 (dd, 1H, J 6.3, 1.2, CH}_\text{alkene}\text{), 4.60-4.56 (m, 1H, CHOTBS), 3.96 (d, 1H, J 2.7, CHOH), 2.16-2.14 (br s, 1H, OH), 0.78 (s, 9H, C(CH}_3\text{)3), 0.04 (s, 3H, SiCH}_3\text{), 0.00 (s, 3H, SiCH}_3\text{);} \]
\[ ^{13}C \text{ (75MHz, CDCl}_3\text{) } \delta_C 203.0 \text{ (C=O), 158.9 (CH), 133.0 (CH), 82.7 (CH), 78.0 (CH), 26.2 (3 x CH}_3\text{), 18.8 (C), -4.1 (CH}_3\text{), -4.7 (CH}_3\text{).} \]

84:
\[ \alpha_D^{22} -155 \text{ (c 1.02 in CHCl}_3\text{)}; \]
\[ \nu_{\text{max}} \text{ (cm}^{-1}) \text{ 2930, 2858, 1742, 1473, 1370}; \]
\[ ^1H \text{ (300MHz, CDCl}_3\text{) } \delta_H 7.23 \text{ (dd, 1H, J 6.2, 1.7, CH}_\text{alkene}\text{), 6.17 (d, 1H, J 6.2, CH}_\text{alkene}\text{), 5.56-5.52 (m, 1H, CHOAc), 4.15 (d, 1H, J 2.6, CHOTBS), 2.01 (s, 3H, CH}_3\text{acetate}, 0.79 (s, 9H, C(CH}_3\text{)3), 0.04 (s, 3H, SiCH}_3\text{), 0.00 (s, 3H, SiCH}_3\text{);} \]
\[ ^{13}C \text{ (75MHz, CDCl}_3\text{) } \delta_C 203.2 \text{ (C), 171.9 (C), 157.0 (CH), 135.8 (CH), 80.5 (CH), 79.8 (CH), 27.3 (3 x CH}_3\text{), 22.5 (CH}_3\text{), 18.1 (C), -3.0 (CH}_3\text{), -3.6 (CH}_3\text{);} \]
HRMS (M+H)+ calcd. for C_{13}H_{23}O_4Si 271.1365, found m/z 271.1369.
To a solution of 87 (20.0 g, 72.6 mmol) in Et₂O (240 mL) at -78 °C was added dropwise a 1 M solution of DIBAL in toluene (145.2 mL, 145.2 mmol). The stirring was continued for 3 h at 0 °C until completion and then the reaction carefully quenched with saturated Rochelle salt solution (80 mL). The reaction mixture was stirred for a further 45 min and then extracted with Et₂O (3 x 100 mL), washed with brine (2 x 50 mL), dried over magnesium sulfate, filtered and concentrated in vacuo. Flash column chromatography eluting with Et₂O (10%)/PE gave the allylic alcohol 114 (16.4 g, 98%) as a colourless oil.

ν<sub>max</sub> (film)/cm<sup>-1</sup> 3591, 3350, 2960, 2852, 2142;

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ<sub>H</sub> 6.36 (s, 1H, CH<sub>alkene</sub>), 4.37-4.35 (m, 2H, CH<sub>2</sub>), 2.11 (br. s, 1H, OH), 0.27 (s, 9H, CH<sub>3</sub>);

<sup>13</sup>C (75MHz, CDCl<sub>3</sub>) δ<sub>C</sub> 137.6 (CH<sub>alkene</sub>), 110.9 (C<sub>alkene</sub>), 102.3 (C), 100.8 (C), 67.8 (CH<sub>2</sub>), 0.0 (3 x CH<sub>3</sub>).
(1,1-Dimethylethyl)(2-bromo-2-pentene-5-trimethylsilyl-4-ynyl)oxy)diphenylsilane 115

![](image)

To a solution of 114 (16.0 g, 69 mmol) in DMF (80 mL) at 0 °C was added successively imidazole (5.6 g, 83 mmol) and tert-butyldiphenylsilyl chloride (19.6 mL, 76 mmol). The reaction was stirred for 2 h and quenched with a saturated aqueous solution of NaHCO₃ (50 mL). The reaction mixture was extracted with Et₂O (3 x 300 mL), washed with H₂O (2 x 100 mL) and brine (50 mL), dried over magnesium sulfate, filtered and concentrated in vacuo. Flash column chromatography eluting with Et₂O (5%)/PE gave 115 (30.7 g, 95%) as a colourless oil.

ν max (film)/cm⁻¹ 3072, 2959, 2931, 2896, 2858, 2144;
¹H NMR (300 MHz, CDCl₃) δH 7.65-7.63 (m, 4H, CH₆), 7.47-7.37 (m, 6H, CH₆), 6.57 (s, 1H, CH₆alkene), 4.31 (s, 2H, CH₂), 1.26 (s, 9H, CH₃TBDPS), 0.19 (s, 9H, CH₃TMS);
¹³C (75MHz, CDCl₃) δC 136.8 (CH₆alkene), 136.4 (CH₆), 132.6 (CH₆Ar), 130.2 (CH₆Ar), 128.0 (CH₆Ar), 109.1 (C₆alkene), 101.4 (C), 101.3 (C), 68.0 (CH₂), 26.8 (3 x CH₃TBDPS), 19.4 (C₇TBDPS), 0.0 (3 x CH₃TMS).
(1,1-Dimethylethyl)[(2-bromo-2-penten-4-ynyl)oxy]diphenylsilane 116

To a solution of 115 (20.0 g, 42.4 mmol) in methanol (210 mL) was added K$_2$CO$_3$ (0.6 g, 4.2 mmol) and the reaction was stirred for 2 h. The mixture was concentrated in vacuo and then the residue was diluted with Et$_2$O (300 mL), washed with brine (2 x 50 mL), dried over magnesium sulfate, filtered and concentrated in vacuo. Flash column chromatography eluting with Et$_2$O (5%)/PE gave 116 (12.6 g, 75%) as a white solid.

$\nu_{\text{max}}$ (film)/cm$^{-1}$ 3266, 2959, 2931, 2882, 2858, 2197;

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$H 7.58-7.56 (m, 4H, CH$_{Ar}$), 7.41-7.30 (m, 6H, CH$_{Ar}$), 6.46-6.44 (m, 1H, CH$_{alkene}$), 4.25-4.24 (m, 2H, CH$_2$), 3.23 (d, 1H, J 2.2, CH$_{alkyne}$) 1.00 (s, 9H, CH$_3$TBDPS);

$^{13}$C (75MHz, CDCl$_3$) $\delta$C 137.7 (CH$_{alkene}$), 135.8 (CH$_{Ar}$), 133.0 (CH$_{Ar}$), 130.5 (CH$_{Ar}$), 128.4 (CH$_{Ar}$), 108.5 (C$_{alkene}$), 83.7 (C), 80.4 (C), 68.3 (CH$_2$), 27.1 (3 x CH$_3$TBDPS), 19.7 (C$_{TBDPS}$).
(1,1-Dimethylethyl)[(2-bromo-6,6-dimethoxy-2-hexen-4-ynyl)oxy]diphenylsilane

A solution of 116 (10.0 g, 25 mmol) and ZnCl₂ (3.4 g, 25 mmol) in trimethylorthoformate (156 mL) in a Dean-Stark apparatus was heated at 160 °C for 10 h. The reaction mixture was allowed to cool to rt and then filtered through celite and washed with Et₂O (500 mL). The filtrate was concentrated in vacuo and purified by flash column chromatography eluting with Et₂O (10%)/PE to give 117 (9.8 g, 83%) as a brown oil.

νmax (film)/cm⁻¹ 3082, 2955, 2931, 2892, 2828, 2225;

¹H NMR (300 MHz, CDCl₃) δH 7.58-7.55 (m, 4H, CHAr), 7.38-7.30 (m, 6H, CHAr), 6.52-6.51 (m, 1H, CHalkene), 5.26 (d, 1H, J 1.5, CH(OMe)₂), 4.25 (d, 2H, J 1.5, CH₂), 3.37 (s, 6H, OCH₃) 0.99 (s, 9H, CH₃TBDPS);

¹³C (75MHz, CDCl₃) δC 137.9 (CHalkene), 135.8 (CHAr), 132.9 (CHAr), 130.5 (CHAr), 128.3 (CHAr), 108.2 (Calkene), 93.9 ((MeO)₂CH), 89.7 (C), 82.7 (C), 68.3 (CH₂), 53.1 (2 x CH₃), 27.1 (3 x CH₃TBDPS), 19.7 (C₃TBDPS).
(1,1-Dimethylethyl)(2-(2-(1,1,1-trimethylsilyl)ethynyl)-6,6-dimethoxy-2-hexen-4-ylnyl)oxy)diphenylsilane 118

A degassed solution of 117 (9.8 g, 20.7 mmol), n-propylamine (2.7 mL, 33.1 mmol) and trimethylsilylacetylene (4.4 mL, 31.0 mmol) in THF (200 mL) was added to a suspension of CuI (0.2 g, 1.8 mmol) and (PPh₃)₂PdCl₂ (0.6 g, 0.8 mmol) in THF (10 mL) and heated at 60 °C. The stirring was continued for 4 h and then the reaction allowed to cool to rt and quenched with a saturated aqueous solution of NH₄Cl (80 mL). The reaction mixture was extracted with Et₂O (3 x 100 mL), washed with brine (50 mL), dried over magnesium sulfate, filtered and concentrated *in vacuo*. Flash chromatography eluting with (5%)/PE gave the title compound 118 (8.5 g, 80%) as a yellow oil.


\[ \nu_{\text{max}} \text{ (film)/cm}^{-1} \] 3075, 2996, 2958, 2892, 2828, 2215;

\[ ^1\text{H NMR (300 MHz, CDCl}_3 \] \( \delta \) 7.65-7.62 (m, 4H, CH₂), 7.45-7.35 (m, 6H, CH₂), 6.28-6.27 (m, 1H, CH₃), 5.34 (d, 1H, J 1.5, CH(OMe)₂), 4.22 (d, 2H, J 1.5, CH₂), 3.42 (s, 6H, OCH₃) 1.04 (s, 9H, CH₃OTBDPS), 0.15 (s, 9H, CH₃TMS);

\[ ^{13}\text{C (75MHz, CDCl}_3 \] \( \delta \) 136.2 (CH₃), 135.7 (2 x CH₂), 133.1 (2 x CH₃), 130.2 (2 x CH₂), 128.2 (2 x CH₂), 128.1 (2 x CH₃), 112.7 (Calkene), 103.9 (C), 100.8 (C), 93.9 ((MeO)₂CH), 90.1 (C), 83.8 (C), 65.3 (CH₂), 52.9 (2 x CH₃), 27.0 (3 x CH₃OTBDPS), 19.5 (C-TBDPS), 0.0 (CH₃TMS).
2-Ethynyl-6,6-dimethoxy-hex-2-en-4-yn-1-ol 112

To 118 (2.5 g, 8.5 mmol) in THF (15 mL) was added a 1 M solution of TBAF in THF (1.7 mL, 17.0 mmol) and the reaction was stirred for 1 h. The reaction mixture was then quenched with H$_2$O (5 mL) and extracted with Et$_2$O (2 × 10 mL), washed with brine (5 mL), dried over magnesium sulfate, filtered and concentrated in vacuo. Flash column chromatography eluting with Et$_2$O (20%)/PE gave 112 (1.47 g, 96%) as a clear yellow oil.

$\nu_{\text{max}}$ (film)/cm$^{-1}$ 3591, 3216, 2225, 2182, 1360;

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$H 6.20 (s, 1H, CH$_{\text{alkene}}$), 5.42 (s, 1H, (MeO$_2$)CH), 4.33 (d, 2H, $J$ 1.5, CH$_2$OH), 3.55 (br. s, 7H, 2 x CH$_3$ and H$_{\text{alkyne}}$), 2.41 (br. s, 1H, OH);

$^{13}$C (75MHz, CDCl$_3$) $\delta$C  128.0 (CH$_{\text{alkene}}$), 116.7 (C$_{\text{alkene}}$), 95.7 (CH$_{\text{alkyne}}$), 93.0 ((MeO)$_2$CH), 88.4 (C), 84.8 (C), 82.3 (C), 66.9 (CH$_2$), 54.9 (2 x CH$_3$);

HRMS (M+H)$^+$ cald. for C$_{10}$H$_{13}$O$_3$ 181.078, found $m/z$ 181.081.
(2R,3S)-[3-(3,3-Dimethoxy-prop-1-ynyl)-2-ethynyl-oxiranyl]-methanol 119

To a suspension of activated powdered molecular sieves 4Å (1.3 g) in DCM (3.5 mL) cooled at -25 °C was added Ti(i-PrO)₄ (0.65 mL, 2.20 mmol) and d-(-)-diethyl tartrate (0.38 mL, 2.20 mmol) and the reaction mixture was stirred for 30 min. A prepared solution of 5.2 M of tert-butyl hydroperoxide in DCM (7 mL, 37.8 mmol) was added dropwise and the reaction was stirred for 10 min. The enediyne 111 (2.0 g, 11.0 mmol) was added dropwise then the reaction mixture was allowed to warm to -6 °C and stirred for 96 h. The reaction was quenched with a saturated solution of sodium thiosulfate (25 mL) and diluted with Et₂O (25 mL). The resulting precipitate was filtered through celite and washed with Et₂O (200 mL). The filtrate was extracted with Et₂O (3 x 50 mL), washed with brine (20 mL), dried over magnesium sulfate, filtered and concentrated in vacuo. Flash column chromatography eluting with Et₂O (10%)/PE gave the enantiomer 119 (200 mg, 10%) as a colourless oil.

α_D^22 +21.1 (c 1.0 in CHCl₃);
ν_max (film)/cm⁻¹ 3425, 2202, 1630;
H NMR (300 MHz, CDCl₃) δ_H 5.13 (s, 1H, (MeO)₂CH), 3.90 (d, 1H, J 13.0, CH₂OH), 3.79 (d, 1H, J 13.0, CH₂OH), 3.70 (s, 1H, H_alkyne), 3.30 (s, 6H, CH₃), 2.45 (s, 1H, CH_epoxy), 1.80 (br. s, 1H, OH);
C (75MHz, CDCl₃) δ_C 93.2 ((MeO)₂CH), 81.3 (C), 80.1 (C), 77.0 (C), 76.2 (CH_alkyne), 62.3 (CH₂), 57.9 (C_epoxy), 53.1 (2 x CH₃), 48.3 (CH_epoxy);
HRMS (M+NH₄)⁺ cald. for C₁₀H₁₆NO₄ 214.1079, found m/z 214.1080.
(4S)-4-(2,2-Dibromo-vinyl)-2,2-dimethyl-[1,3]-dioxolane 131

To a solution of 1,2-5,6-diisopropylidene-D-mannitol 92 (25.0 g, 95 mmol) in DCM (350 mL) and aqueous sodium bicarbonate (4 mL) was added portionwise sodium periodate (41.2 g, 190 mmol) over 20 min. Then the reaction mixture was stirred for 2 h and filtered through a pad of magnesium sulfate. DCM was then evaporated under vacuum (cold bath) to give the D-glyceraldehyde acetonide 34.

Meanwhile, to a solution of carbon tetrabromide (25.3 g, 77 mmol) in DCM (100 mL) at 0 °C, was added triphenylphosphine (40.3 g, 154 mmol). The reaction mixture was stirred for 30 min and a solution of 34 (24.7 g, 190 mmol) in DCM (250 mL) was added over a period of 30 min. Stirring was continued for 1 h and the suspension was then poured into PE (2 L) giving a precipitation of an orange/brown semi-crystalline mass. The supernatant liquid was decanted, and the resulting solid was washed with Et₂O (100 mL) and PE (100 mL). The filtrate was concentrated in vacuo to give an oil contaminated with triphenylphosphine oxide. Flash column chromatography eluting with Et₂O 3%/PE gave the vinyl dibromide 131 (7.09 g, 75%) as a yellow oil.

¹H NMR (300 MHz, CDCl₃) δH 6.53 (d, 1H, J 7.6, CHalkene), 4.72 (t, 1H, J 6.5, CHCH₂), 4.18 (dd, 1H, J 8.4, 6.3, CHCH₂), 3.68 (dd, 1H, J 8.4, 6.5, CHCH₂), 1.42 (s, 3H, CH₃), 1.38 (s, 3H, CH₃);

¹³C (75MHz, CDCl₃) δC 137 (CH), 110.0 (C), 92.6 (CBr), 76.1 (CH), 68.0 (CH₂), 26.6 (CH₃), 25.6 (CH₃);

HRMS (M+H)+ calcd. for C₇H₁₁O₂⁷⁹Br₂ 284.91258, found m/z 284.91248.
(4S)-(2,2-Dimethyl-[1,3]dioxolan-4-yl)-propynoic acid methyl ester 12089

\[ \text{CO}_2\text{Me} \]

To a solution of dibromide 131 (10.0 g, 35.0 mmol) in THF (170 mL) at -78 °C was added \( n \)-BuLi (32.0 mL of a 2.3 M solution in hexanes, 73.4 mmol) over 30 min. The stirring was continued for 2 h and then methyl chloroformate (5.4 mL, 69.9 mmol) was added slowly. After stirring for 30 min, the reaction was warmed to rt and quenched with a saturated aqueous solution of NaHCO₃. The mixture was extracted with Et₂O (3 x 150 mL), washed with brine (75 mL), dried over magnesium sulfate, filtered and concentrated \textit{in vacuo}. Flash column chromatography eluting with Et₂O (10%)/PE gave the title compound 120 (5.1 g, 79%) as a colourless oil;

\[ ^1\text{H} \text{NMR (300 MHz, CDCl}_3\text{)} \delta_H 4.80 (1H, dd, J 6.5, 5.5, CHCH}_2\text{), 4.18 (1H, dd, J 8.3, 6.5, CHCH}_2\text{), 4.02 (1H, dd, J 8.3, 5.5, CHCH}_2\text{), 3.77 (3H, s, CH}_3\text{ester), 1.48 (3H, s, CH}_3\text{), 1.37 (3H, s, CH}_3\text{);} \]

\[ ^13\text{C} \text{ (75MHz, CDCl}_3\text{)} \delta_C 153.4 (\text{C}=\text{O}), 111.2 (\text{C}), 84.8 (\text{C}), 76.7 (\text{C}), 69.2 (\text{CH}_2), 64.9 (\text{CH}), 52.8 (\text{CH}_3), 26.0 (\text{CH}_3), 25.7 (\text{CH}_3); \]

\[ m/z 185 (\text{M}+\text{H}^+, 7\%), 157, 137, 129, 111, 97, 83, 69, 61. \]
(4R)-3-(2,2-Dimethyl-[1,3]dioxolan-4-yl)-3-iodo-acrylic acid methyl ester 121

![Chemical structure](image)

To a solution of 120 (1.00 g, 5.4 mmol) in acetonitrile (120 mL) at 175 °C was added sodium iodide (1.22 g, 8.1 mmol) and acetic acid (0.52 mL, 8.6 mmol). The stirring was continued for 90 min at this temperature and the reaction mixture was carefully poured into a mixture of a saturated solution of NaHCO₃ (50 mL) and Et₂O (150 mL). The resulting suspension was extracted with Et₂O (3 x 100 mL), washed with a saturated aqueous solution of NaHCO₃ (50 mL) and brine (50 mL), dried over magnesium sulfate and concentrated in vacuo. Flash column chromatography eluting with Et₂O (10%)/PE gave the vinyl iodide 121 (1.23 g, 95%) as a yellow oil.

αD²² +40.1 (c 1.01 in CHCl₃);

νmax (film)/cm⁻¹ 2988, 2950, 2880, 1732, 1630, 1455, 1434, 1377;

¹H NMR (300 MHz, CDCl₃) δH 6.87 (d, 1H, J 1.6, CHalkene), 4.74 (t, 1H, J 6.8, CHCH₂), 4.34 (dd, 1H, J 8.6, 6.8, CHCH₂), 3.81 (dd, 1H, J 8.6, 6.8, CHCH₂), 3.76 (s, 3H, CH₃ester), 1.47 (s, 3H, CH₃), 1.40 (s, 3H, CH₃);

¹³C (75MHz, CDCl₃) δC 164.8 (C=O), 123.2 (CHalkene), 118.5 (Calkene), 111.7 (Me₂C), 82.9 (CH), 69.9 (CH₂), 51.7 (CH₃ester), 26.0 (CH₃), 25.8 (CH₃);

HRMS (M+H)⁺ cald. for C₉H₁₄O₄I 312.99368, found m/z 312.99371.

(4S)-3-(2,2-Dimethyl-[1,3]dioxolan-4-yl)-5-trimethylsilyl-pent-2-en-4-ynoic
cacid methyl ester $127^{47,86}$

A degassed solution of $121$ (3.0 g, 9.60 mmol), Et$_3$N (4.0 mL, 28.80 mmol) and trimethylsilylacetylene (1.9 mL, 13.50 mmol) in acetonitrile (75 mL) was added to a suspension of CuI (183 mg, 0.96 mmol) and Pd(PPh)$_3$$_4$ (555 mg, 0.48 mmol) in acetonitrile (10 mL) at rt. The reaction was continued for 2 h and a mixture of saturated aqueous solution of NH$_4$Cl (20 mL) and Et$_2$O (100 mL) was added. The reaction mixture was extracted with Et$_2$O (3 x 100 mL), washed with brine (50 mL), dried over magnesium sulfate, filtered and concentrated in vacuo. Flash column chromatography eluting with Et$_2$O (10%)/PE gave the title compound $127$ (2.5 g, 91%) as a yellow oil.

$\alpha_D^{22}$ +32.6 ($c$ 1.01 in CHCl$_3$);

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$H 6.37 (d, 1H, J 1.5, CH$_{alkene}$), 4.61 (dt, 1H, J 6.8, 1.5, CHCH$_2$), 4.25 (dd, 1H, J 8.5, 6.8, CHCH$_2$), 3.92 (dd, 1H, J 8.5, 6.8, CHCH$_2$), 3.74 (s, 3H, CH$_3$), 1.45 (s, 3H, CH$_3$), 1.41 (s, 3H, CH$_3$), 0.23 (s, 9H, SiCH$_3$);

$^{13}$C (75MHz, CDCl$_3$) $\delta$C (ppm) 165.2 (C–O), 136.9 (CH), 123.7 (C), 110.9 (C), 109.0 (C), 99.4 (C), 77.7 (CH), 69.1 (CH$_2$), 51.4 (CH$_3$), 26.2 (CH$_3$), 25.8 (CH$_3$), -0.4 (3 x CH$_3$);

HRMS (M+H)$^+$ calcd. for C$_{14}$H$_{23}$O$_4$Si 283.13656, found m/z 283.13657.
To a solution of 127 (2.5 g, 8.7 mmol) in THF (35 mL) at −78 °C was added dropwise a 1 M solution of DIBAL in toluene (21.8 mL, 21.8 mmol). The stirring was continued for 3 h until completion and then the reaction quenched with saturated Rochelle salt solution (10 mL). The reaction mixture was stirred for further 45 min and then extracted with Et₂O (2 x 30 mL), washed with brine (2 x 10 mL), dried over magnesium sulfate, filtered and concentrated *in vacuo*. Flash column chromatography eluting with Et₂O (40%)/PE gave the allylic alcohol 132 (2.2 g, 98%) as a yellow oil.

α_D^{22} +29.6 (c 2.07 in CHCl₃);

^1^H NMR (300 MHz, CDCl₃) δ_H 6.25 (t, 1H, J 6.4, CH_alkene), 4.49 (t, 1H, J 6.8, CHCH₂), 4.40 (d, 2H, J 6.4, CH₂OH), 4.14 (dd, 1H, J 8.3, 6.8, CHCH₂), (dd, 1H, J 8.3, 6.8, CHCH₂), 1.62 (br. s, 1H, OH), 1.46 (s, 3H, CH₃), 1.40 (s, 3H, CH₃), 0.20 (s, 9H, CH₃Si);

^1^C (75MHz, CDCl₃) δ_C 138.8 (CH), 123.7 (C), 110.2 (C), 103.0 (C), 99.2 (C), 78.0 (CH), 68.9 (CH₂), 61.3 (CH₂), 26.5 (CH₃), 26.2 (CH₃), 0.00 (3 x CH₃);

HRMS (M+H)^+ cald. for C_{13}H_{23}O_{3}Si 255.1416, found m/z 255.1415.
(4S)-3-(2,2-Dimethyl-[1,3]dioxolan-4-yl)-pent-2-en-4-yn-1-ol 133

To a solution of 132 (200 mg, 0.8 mmol) in dry THF (5 mL) was added a 1 M solution of TBAF in THF (1.6 mL, 1.6 mmol) and the reaction stirred for 20 min. The reaction was poured into H₂O (2 mL). The mixture was extracted with Et₂O (3 x 15 mL) and the combined organics washed with brine (5 mL), dried over magnesium sulfate, filtered and concentrated in vacuo. Flash column chromatography eluting with Et₂O 50%/PE afforded 133 (122 mg, 85%) as a yellow oil.

α₀²² +17.1 (c 1.04 in CHCl₃, λ 589 nm);
ν_max (film)/cm⁻¹ 3411, 3284, 2987, 2940, 2882, 2361, 1457;
¹H NMR (300 MHz, CDCl₃) δH 6.33 (t, 1H, J 6.4, CH₃alkene), 4.53 (dd, 1H, J 7.1, 6.4, CHCH₂), 4.42 (d, 2H, J 6.4, CH₂OH), 4.17 (dd, 1H, J 8.3, 6.4, CHCH₂), 3.90 (dd, 1H, J 8.3, 7.1, CHCH₂), 3.23 (s, 1H, H̵₃alkyne), 1.67 (br s, 1H, OH), 1.47 (s, 3H, CH₃), 1.40 (s, 3H, CH₃);
¹³C (75MHz, CDCl₃) δC 139.2 (CH₃alkene), 122.6 (C), 110.2 (Me₂C), 84.8 (C), 78.1 (CH), 77.6 (CH), 68.7 (CH₂), 60.9 (CH₂OH), 26.3 (CH₃), 25.9 (CH₃);
HRMS (M+H)⁺ cald. for C₁₀H₁₅O₃ 183.1021, found m/z 183.1022.
(2S,3S,4R)-[3-(2,2-Dimethyl-[1,3]dioxolan-4-yl)-3-ethynyl-oxiranyl]-methanol

To a suspension of activated powdered molecular sieves 4Å (2.3 g) in DCM (6 mL) cooled at -25 °C was added Ti(i-PrO)₄ (1.13 ml, 3.78 mmol) and D(-)-diethyl tartrate (0.65 ml, 3.78 mmol) and the reaction mixture was stirred for 30 min. A prepared solution of 5.2 M of tert-butyl hydroperoxide in DCM (18 mL, 94.5 mmol) was added dropwise and the reaction was stirred for 10 min. 133 (3.447 g, 18.9 mmol) was then added dropwise and the reaction mixture was allowed to warm to -6 °C and stirred for 96 h. The reaction was quenched with a saturated aqueous solution of sodium thiosulfate (50 mL) and diluted with Et₂O (50 mL). The resultant precipitate was filtered through celite and washed with Et₂O (300 mL). The filtrate was extracted with Et₂O (2 x 100 mL), washed with brine (50 mL), dried over magnesium sulfate, filtered and concentrated in vacuo. Flash column chromatography eluting with Et₂O (40%)/PE gave 134 (3.2 g, 81%) as a colourless oil.

α_D^{22} +62.5 (c 1.1 in CHCl₃, λ 589 nm);

ν_max (film)/cm⁻¹ 3452, 3271, 2987, 2921, 2889, 2119, 1377;

¹H NMR (500 MHz, CDCl₃) δ_H 4.13 (dd, 1H, J 8.7, 6.3, CH₂CH), 4.04 (dd, 1H, J 8.7, 6.3, CH₂CH), 3.93 (t, 1H, J 6.3, CH₂CH), 3.90 (dd, 1H, J 12.4, 4.4, CH₂OH), 3.78 (dd, 1H, J 12.4, 6.2, CH₂OH), 3.28 (dd, 1H, J 6.2, 4.4, C epoxy), 2.67 (br s, 1H, OH), 2.45 (s, 1H, H alkene), 1.42 (s, 3H, CH₃), 1.31 (s, 3H, CH₃);

¹³C (125 MHz, CDCl₃) δ_C (ppm) 110.8 (Me₂C), 77.2 (C), 76.6 (CH), 75.7 (C alkene), 66.6 (CH₂), 61.7 (CH₂OH), 61.2 (C epoxy), 55.1 (C epoxy), 26.05 (CH₃), 25.1 (CH₃);

HRMS (M+H)⁺ calcd. for C₁₀H₁₅O₄ 199.09703, found m/z 199.09602;

Anal calcd for CH: C, 60.59; H, 7.12. Found: C, 60.70; H, 7.12.
To 134 (0.50 g, 2.52 mmol) in DCM (13 mL) at 0 °C was added Dess-Martin periodinane (2.02 g, 5.04 mmol) in one portion. The stirring was continued at 0 °C for 30 min and the reaction mixture was poured into a mixture of a saturated aqueous solution of sodium thiosulfate (5 mL) and a saturated aqueous solution of NaHCO₃ (5 mL). Then Et₂O (100 mL) was added and the mixture stirred for 30 min. The mixture was extracted with Et₂O (3 x 50 mL), washed with brine (2 x 10 mL), dried over magnesium sulfate, filtered and concentrated in vacuo. The crude epoxy-aldehyde 136 was seen to be of sufficient purity (without flash chromatography) for use in the next stage.

To a solution of carbon tetrabromide (1.68 g, 5.04 mmol) in DCM (50 mL) was added triphenylphosphine (1.32 g, 5.04 mmol) and the reaction mixture was stirred for 15 min at -78 °C. A solution of 136 and Et₃N (0.53 mL, 3.78 mmol) in DCM (30 mL) was added dropwise via cannula. The stirring was continued for 10 min and the reaction quenched with a saturated aqueous solution of NaHCO₃. The reaction mixture was extracted with DCM, washed with brine, dried over magnesium sulfate, filtered and concentrated in vacuo. The resulting crude product was transferred on silica gel previously neutralised with 0.2% of Et₃N. Flash column chromatography eluting with Et₂O 10%/PE gave the epoxy-dibromoalkene 137 (0.47 g, 53%) as a colourless oil.
$\alpha_D^{22} + 94$ (c 1 in CHCl$_3$);

$v_{\text{max}}$ (cm$^{-1}$) 3225, 2917, 2856, 2172, 1465;

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$H 6.39 (d, 1H, $J$ 7.9, CH$_{\text{alkene}}$), 4.15 (dd, 1H, $J$ 10.4, 9.2, CH$_2$CH), 4.034 (dd, 1H, $J$ 9.2, 5.7, CH$_2$CH), 4.032 (dd, 1H, 10.4, 5.7, CH$_2$CH), 3.78 (d, 1H, $J$ 7.9, CH$_{\text{epoxy}}$), 2.50 (s, 1H, H$_{\text{alkyne}}$), 1.42 (3H, s, CH$_3$), 1.31 (s, 3H, CH$_3$);

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$C 132.4 (CH$_{\text{alkyne}}$), 111.0 (Me$_2$C), 96.7 (CBr$_2$), 77.2 (C), 76.5 (C), 75.9 (CH), 66.8 (CH$_2$), 60.2 (CH$_{\text{epoxy}}$), 57.0 (C$_{\text{epoxy}}$), 26.2 (CH$_3$), 25.3 (CH$_3$);

HRMS (M+H)$^+$ cald. for C$_{11}$H$_{13}$Br$_2$O$_3$ 350.9231, found $m/z$ 350.9230.
Dimethyl (diazomethyl)phosphonate 144\textsuperscript{101}

![Chemical Structure](image)

To a solution of dimethyl methylphosphonate 142 (2.0 mL, 18.4 mmol) in THF (40 mL) was added a 2.3 M of a solution of n-BuLi in hexanes (8.0 mL, 18.4 mmol) dropwise at -78 °C and the reaction mixture was stirred for 30 min. 2,2,2-Trifluoroethyl trifluoroacetate (3.7 mL, 27.6 mmol) was added rapidly to the mixture. The stirring was continued for 15 min and warmed to rt. The reaction mixture was poured into a mixture of Et\textsubscript{2}O (250 mL) and 3% of an aqueous solution of HCl (10 mL). The organic portion was washed with a saturated aqueous solution of NaHCO\textsubscript{3} (10 mL) and a saturated aqueous solution of NaCl (10 mL), dried over magnesium sulphate, filtered and concentrated \textit{in vacuo} to give 143 as a pale yellow oil.

To a solution of 4-acetamidobenzensulfonyl azide (3.97 g, 16.5 mmol) in CH\textsubscript{3}CN (40 mL) was added the crude phosphonate 143 and the reaction was cooled to 0 °C. Et\textsubscript{3}N (2.3 mL, 16.5 mmol) was added dropwise and the reaction was stirred for 12 h at rt. Concentration \textit{in vacuo} gave the crude residue to which CHCl\textsubscript{3} (150 mL) was added. The mixture was filtered to remove the 4-acetamidobenzensulfonylamide which was washed with additional CHCl\textsubscript{3} (2 x 50 mL). Purification by flash column chromatography eluting with EtOAc (100%) gave 144 (812 mg, 33%) as a yellow oil.

\text{v}_{\text{max}} (\text{cm}^{-1}) \text{ 3070, 2940, 2850, 2100, 1765, 1657;}

\textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) \delta\textsubscript{H} 4.49 (d, 1H, \textit{J}_{\text{H-P}} 10.7 Hz, PCH); 3.74 (d, 6H, \textit{J}_{\text{H-P}} 11.5 Hz, POCH\textsubscript{3});

\textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) \delta\textsubscript{C} 59.1 (C=N\textsubscript{2}), 53.5 (d, \textit{J}_{\text{C-P}} 5.8 Hz, OCH\textsubscript{3} x 2).
Dimethyl 1-diazo-2-oxoalkylphosphonate 146

\[ \text{MeO} \begin{array}{c} \text{P} \\text{MeO} \\ \text{N}_2 \end{array} \text{O} \]

To a solution a suspension NaH (75.6 mg, 3.1 mmol) in benzene (9 mL) and THF (1.5 mL) was added dimethyl 2-oxopropylphosphonate 145 (0.42 mL, 3.0 mmol) at 0 °C and the reaction was stirred for 1 h. A solution of tosyl azide (623 mg, 3.1 mmol) in benzene (1.5 mL) was added and the reaction was warmed to rt. Stirring was continued for 2 h and the mixture filtered through celite and concentrated in vacuo. Purification by flash column chromatography eluting with EtOAc (50%)/PE gave 146 (467 mg, 81%).

\[ \text{v}_{\text{max}} \ (\text{cm}^{-1}) \ 2950, \ 2849, \ 2221, \ 2120, \ 1736, \ 1652; \]
\[ ^1\text{H} \text{ NMR} \ (400 \text{ MHz, CDCl}_3) \ \delta_H \ 3.81 \ (d, \ 6\text{H, }^3J_{\text{H,P}} \ 11.9 \text{ Hz, OCH}_3), \ 2.24 \ (s, \ 3\text{H, CH}_3); \]
\[ ^{13}\text{C} \text{ NMR} \ (100 \text{ MHz, CDCl}_3) \ \delta_C \ 190.3 \ (d, ^2J_{\text{C,P}} \ 3.2 \text{ Hz, C=O}), \ 60.8 \ (\text{br, C=N}_2), \ 54.0 \ (d, ^3J_{\text{C,P}} \ 5.8 \text{ Hz, 2 x OCH}_3), \ 27.5 \ (\text{CH}_3). \]
(2,2-Dimethoxy-ethyl)-phosphonic acid dimethyl ester 150

To a solution of trimethyl phosphite (10 mL, 85 mmol) was added bromo-1,1-dimethoxyethane (10 mL, 85 mmol) at 130 °C and the reaction was stirred for 2 h. Purification by flash column chromatography eluting with EtOAc (70%)/PE gave 150 as a colourless oil.

νmax (cm⁻¹) 2980, 2870;
¹H NMR (300 MHz, CDCl₃) δH 4.63 (dd, 1H, J 10.9, 5.6, CH), 3.92 (q, 4H, J 7.15, CH₂O), 3.18 (s, 6H, CH₃O), 2.02 (dd, 2H, J 18.7, 5.6, CH₂P), 1.18 (t, 6H, J 6.8, CH₃E);
¹³C NMR (75 MHz, CDCl₃) δC 99.8 (CH), 61.5 (CH₂), 52.7 (2 x CH₃), 31.5 (CH₂), 29.7 (CH₂), 16.2 (2 x CH₃).
(4R)-2,2-Dimethyl-[1,3]dioxolane-4-yl)-3-trimethylsilyl-prop-2-yn-1-ol 172

To a solution of 1,2,5,6-diisopropylidene-D-mannitol 92 (25.0 g, 95 mmol) in DCM (350 mL) and aqueous sodium bicarbonate (4 mL) was added portionwise sodium periodate (41 g, 190 mmol) over 20 min. Then the reaction mixture was stirred for 2 h and filtered through a pad of magnesium sulfate. DCM was then evaporated under vacum in a cold bath (28 °C) to give the D-glyceraldehyde acetone 34.

Meanwhile to a solution of trimethylsilylacetylene (32 mL, 228 mmol) in THF (900 mL) was added freshly made lithium hexamethyldisilazide (209 mL, 209 mmol) at -78 °C. The reaction mixture was stirred for 30 min and a solution of 34 (24.7 g, 190 mmol) in THF (250 mL) was added over a period of 30 min. The reaction was stirred for 30 min and quenched with a saturated aqueous solution of NH₄Cl (150 mL). The reaction mixture was concentrated in vacuo to a volume of approximately 300 mL and diluted with EtOAc (300 mL). The mixture was washed with a saturated aqueous solution of NH₄Cl (250 mL) and H₂O (250 mL), and the combined aqueous portions were extracted with EtOAc (150 mL). The organics were washed with brine (100 mL), dried over magnesium sulfate, filtered and concentrated in vacuo. Flash column chromatography in EtOAc (20%)/PE afforded the inseparable diastereomeric propargylic alcohols 172 (1.2:1, 35.4 g, 81%) as a pale yellow oil.

vmax (cm⁻¹) 3434, 2990, 2962, 2252, 1456, 1374;

¹H NMR (300 MHz, CDCl₃) δH 4.33-3.71 (m, 4H, CH₂O-CHO-CHOH), 2.64 (br. s, 1H, OH, major only), 2.50 (br. s, 1H, OH, minor only), 1.28 (3H, s, CH₃), 1.21 (s, 3H, CH₃), 0.00 (s, 9H, SiCH₃);
$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$C 110.8 (Me$_2$C), 110.4 (Me$_2$C), 102.7 (C), 102.6 (C), 91.7 (C), 91.6 (C), 79.1 (CH$_{\text{OH}}$), 78.1 (CH$_{\text{OH}}$), 66.5 (CH$_2$), 65.4 (CH$_2$), 65.1 (CH), 63.0 (CH), 27.1 (CH$_3$), 26.6 (CH$_3$), 25.6 (2 x CH$_3$), 0.4 (6 x CH$_3$);

HRMS (M+NH$_4^+$) calcd. for C$_{11}$H$_{24}$NO$_3$Si 246.1520, found $m/z$ 246.1517.
(4R)-1-(2,2)-Dimethyl-[1,3]dioxolan-4-yl)-3-trimethylsilyl-propynone 35^{1a}

Method A: To pyridinium dichromate (66.0 g, 175.2 mmol) and crushed 3Å molecular sieves (40 g) in DCM (150 mL) was added dropwise a solution of propargylic alcohol 172 (20 g, 87.6 mmol) in DCM (75 mL) and the reaction mixture was stirred for 4 h. Celite (40 g) was then added and the suspension was stirred for 30 min. The reaction mixture was then filtered through a plug of celite and diluted with Et₂O (400 mL). The filtrate was washed with saturated aqueous potassium hydrogen sulfate (3 × 100 mL), saturated aqueous NaHCO₃ (100 mL) and brine (2 × 50 mL), then dried over magnesium sulfate, filtered and concentrated in vacuo. Flash column chromatography eluting with Et₂O (25%)/PE afforded the ynone 35 (16.2 g, 82%).

Method B: To 172 (5.1 g, 22 mmol) in DCM (110 mL) at 0 °C was added Dess-Martin periodinane (18.2 g, 44 mmol) in one portion. The stirring was continued at rt for 6 h and the reaction mixture was poured into a mixture of a saturated aqueous solution of sodium thiosulfate (10 mL) and a saturated aqueous solution of NaHCO₃ (10 mL). Then Et₂O (150 mL) was added and the mixture stirred for 30 min. The mixture was extracted with Et₂O (2 × 100 mL), washed with brine (50 mL), dried over magnesium sulfate, filtered and concentrated in vacuo. Flash column chromatography eluting with Et₂O (25%)/PE afforded the ynone 35 (4.7 g, 95%). Alternatively the crude propargylic ketone, which was seen to be of sufficient purity (without flash chromatography) for use in further stages, was stored at -20 °C in dry THF for later use.
vmax (cm⁻¹) 2989, 2963, 2902, 2153, 1677, 1373;

¹H NMR (300 MHz, CDCl₃) δH 4.28 (1H, dd, J 7.4, 5.0, CHCH₂), 4.0 (1H, dd, J 8.8, 7.4, CHCH₂), 3.91 (1H, dd, J 8.8, 5.0, CHCH₂), 1.27 (3H, s, CH₃), 1.15 (3H, s, CH₃), 0.00 (9H, s, CH₃Si);

¹³C NMR (75 MHz, CDCl₃) δC 187.5 (C=O) 112.8 (C), 104.6 (C), 100.7 (C), 81.8 (CH), 67.8 (CH₂), 27.0 (CH₃), 26.3 (CH₃), 0.0 (3 x CH₃);

HRMS (M+NH₄)⁺ cald. for C₁₁H₂₀NO₃Si 244.1363, found m/z 244.1363.
(3-Chloroprop-1-ynyl)trimethylsilane 156\textsuperscript{107}

\[
\begin{array}{c}
\text{Cl} \\
\equiv \\
\text{TMS}
\end{array}
\]

To propargyl chloride (5.0 mL, 69 mmol) in THF (200 mL) at -78 °C was added dropwise a 1.4 M solution of \(n\)-BuLi in hexane (25 mL, 35 mmol) over 2 h. TMSCl (8.8 mL, 69 mmol) was then added dropwise and the solution allowed to warm to rt and stirred for 1 h. The reaction mixture was quenched with \(\text{H}_2\text{O}\) (200 mL), then \(\text{Et}_2\text{O}\) (200 mL) was added. The aqueous layer was washed with \(\text{Et}_2\text{O}\) (2 \(\times\) 200 mL) and the combined organic extracts washed with \(\text{H}_2\text{O}\) (100 mL), brine (100 mL), and dried over magnesium sulfate, filtered and concentrated \textit{in vacuo}. Purification \textit{via} distillation (bp 135 °C) gave 156 (4.8 g, 48\%) as a colourless oil.

\(\nu_{\text{max}}\) (film)/cm\(^{-1}\) 2962, 2183, 1269, 1029;

\(^1\)H NMR (300 MHz; CDCl\(_3\)) \(\delta\)H 4.13 (s, 2H, CH\(_2\)), 0.18 (s, 9H, CH\(_3\));

\(^13\)C NMR (75 MHz; CDCl\(_3\)) \(\delta\)C 99.6 (C), 91.8 (C), 30.7 (CH\(_2\)), -0.4 (3 x CH\(_3\)).
2-Ethynyl-3-hept-1-yln-oxirane 170 and 171

To ZnBr$_2$ (0.306 g, 1.36 mmol) in THF (1 mL) at -20 °C was added 156 (0.100 g, 0.68 mmol), then the mixture cooled to -78 °C and freshly prepared LDA (1.36 mmol) in THF (3 mL) was added. The mixture was stirred for 1 h then 2-Octynal (0.093 g, 0.75 mmol) was added. The stirring was continued for 1 h at -78 °C and the reaction was warmed to -30 °C and stirred for 45 min. The reaction was poured into a mixture of a saturated aqueous solution of NH$_4$Cl (5 mL) and H$_2$O (20 mL) and then diluted with Et$_2$O (50 mL). The aqueous layer was washed with Et$_2$O (2 × 50 mL) and the combined organic extracts washed with H$_2$O (20 mL), brine (20 mL), dried over magnesium sulfate and filtered. Concentration *in vacuo* gave the crude chlorohydrins 168 and 169 to which DMF (3.5 mL) was added followed by addition of KF (2.73 mmol, 0.158 g) in one portion. The reaction mixture was stirred for 1 h and then quenched with H$_2$O (1 mL). The mixture was extracted with Et$_2$O (20 mL), washed with brine (2 × 10 mL), dried over magnesium sulfate, filtered and concentrated *in vacuo*. Column chromatography eluting with CHCl$_3$ (50%)/PE afforded the crude desilylated chlorohydrins.

To the crude chlorohydrins in DCM (2.5 mL) was added DBU (3.4 mmol, 0.519 g) and the reaction mixture was stirred for 2 h. The mixture was poured on silica gel previously neutralised with DBU (0.1%) in PE. Flash column chromatography eluting with CHCl$_3$ (30%)/PE resulted in the inseparable diastereoisomeric epoxydyynes 170 and 171 (42 %, *trans / cis*: 5 / 3). Repeated column chromatography allowed a small amount of each diastereoisomer to be isolated for analysis.
\( \nu_{\text{max}}(\text{film})/\text{cm}^{-1} \) 3298, 2956, 2933, 2871, 2860, 2237, 2171, 1460, 1398, 1315;

**trans-epoxydiyne (major) 170:**

\(^{1}H\) NMR (300 MHz, CDCl\(_3\)) \( \delta_H \) 3.50 (dt, 1H, \( J \) 2.0, 1.7, CH\(_{\text{epoxy}}\)), 3.43 (dd, 1H, \( J \) 2.0, 1.7, CH\(_{\text{epoxy}}\)), 2.33 (d, 1H, \( J \) 1.7, H\(_{\text{alkyne}}\)), 2.19 (td, 2H, \( J \) 7.1, 1.7, CH\(_{2}\text{propargylic}\)), 1.50 (m, 2H, CH\(_2\)), 1.32 (m, 4H, CH\(_2\)), 0.89 (t, 3H, \( J \) 7.3, CH\(_3\));

\(^{13}C\) NMR (75 MHz, CDCl\(_3\)) \( \delta_C \) 86.0 (C), 79.0 (C), 74.9 (C), 72.4 (CH\(_{\text{alkyne}}\)), 47.3 (CH\(_{\text{epoxy}}\)), 46.7 (CH\(_{\text{epoxy}}\)), 30.9 (CH\(_2\)), 27.8 (CH\(_2\)), 22.1 (CH\(_2\)), 18.6 (CH\(_2\)), 13.9 (CH\(_3\));

**cis-epoxydiyne (minor) 171:**

\(^{1}H\) NMR (300 MHz, CDCl\(_3\)) \( \delta_H \) 3.54 (dt, 1H, \( J \) 3.8, 1.7, CH\(_{\text{epoxy}}\)), 3.50 (dd, 1H, \( J \) 3.8, 1.7, CH\(_{\text{epoxy}}\)), 2.43 (d, 1H, \( J \) 1.7, H\(_{\text{alkyne}}\)), 2.26 (td, 2H, \( J \) 7.1, 1.7, CH\(_{2}\text{propargylic}\)), 1.54 (m, 2H, CH\(_2\)), 1.38 (m, 2H, CH\(_2\)), 1.31 (m, 2H, CH\(_2\)), 0.89 (t, 3H, \( J \) 7.3);

\(^{13}C\) NMR (75 MHz, CDCl\(_3\)) \( \delta_C \) 87.7 (C), 78.2 (C), 77.2 (C), 73.9 (CH\(_{\text{alkyne}}\)), 46.6 (CH\(_{\text{epoxy}}\)), 46.1 (CH\(_{\text{epoxy}}\)), 30.8 (CH\(_2\)), 27.9 (CH\(_2\)), 22.1 (CH\(_2\)), 18.7 (CH\(_2\)), 13.9 (CH\(_3\));

HRMS (M+H\(^+\)) calcd. for C\(_{11}\)H\(_{15}\)O 163.11228, found \( m/\text{z} \) 163.11190.

124
(3-Chloroprop-1-ynyl)triethyilsilane 174

To propargyl chloride (2.5 mL, 34.6 mmol) in THF (100 mL) at -78 °C was added a 1.4 M solution of n-BuLi in hexane (12.5 mL, 17.5 mmol) dropwise over 2 h. TESCl (5.8 mL, 34.6 mmol) was then added dropwise and the solution allowed to warm to rt and stirred for 1 h. The reaction mixture was quenched with H₂O (100 mL), then Et₂O (100 mL) was added. The aqueous layer was then washed with Et₂O (2 × 100 mL) and the combined organic extracts washed with H₂O (50 mL), brine (50 mL), dried over magnesium sulfate, filtered and concentrated \textit{in vacuo}. Flash column chromatography eluting with 100% PE gave 174 (2.4 g, 37%) as a colourless oil.

ν\textsubscript{max}(film)/cm\textsuperscript{-1} 2959, 2179, 1029;

\(^1\)H NMR (300 MHz; CDCl\textsubscript{3}) δ\textsubscript{H} 4.15 (s, 2H, CH\textsubscript{2}Cl), 0.99 (t, 9H, J 7.9, CH\textsubscript{3}), 0.61 (q, 6H, J 7.8, CH\textsubscript{2});

\(^{13}\)C NMR (75 MHz; CDCl\textsubscript{3}) δ\textsubscript{C} 100.8 (C), 89.5 (C), 30.8 (CH\textsubscript{2}), 7.3 (3 x CH\textsubscript{3}), 4.1 (3 x CH\textsubscript{2}).
tert-Butyl-(3-Chloro-prop-1-ynyl)-dimethylsilane 175

To propargyl chloride (5.0 mL, 69 mmol) in THF (200 mL) at -78 °C was added a 2.18 M solution of n-BuLi (16 mL, 35 mmol) dropwise over 2 h. A 2 M solution of TBSCl in THF (34.5 mL, 69 mmol) was then added dropwise via cannula and the reaction was allowed to warm to rt and stirred for 1 h. The reaction was quenched with H₂O (200 mL), extracted with Et₂O (2 x 200 mL), washed with brine (100 mL), dried over magnesium sulfate, filtered and concentrated in vacuo. Column chromatography eluting with 100% PE gave 175 (5.5 g, 42%) as a colourless oil.

ν<sub>max</sub> (cm<sup>−1</sup>) 2916, 2198 1450, 1257, 1033, 817;

<sup>1</sup>H NMR (300 MHz; CDCl₃) δ<sub>H</sub> (300 MHz, CDCl₃) 4.14 (s, 2H, CH₂), 0.94 (s, 9H, C(CH₃)₃), 0.13 (s, 6H, CH₃);

<sup>13</sup>C NMR (75 MHz; CDCl₃) δ<sub>C</sub> 100.3 (C), 90.2 (C), 30.7 (CH₂), 25.9 (C), 16.4 (3 x CH₃), -4.8 (2 x CH₃).
(2S,3S,4R)-[3-(2,2-Dimethyl-[1,3]dioxolan-4-yl)-3-ethynyl-
 oxyranylethynyl]triethyl-silane 16$^{107,47}$

To ZnBr$_2$ (477 mg, 2.1 mmol) in THF (2 mL) at -20 °C was added 174 (200 mg, 1.1 mmol) then the reaction was cooled to -78 °C. A freshly prepared 1M solution of LDA in THF (2.12 mL, 2.1 mmol) was added dropwise and the reaction was stirred for 1 h. The ketone 35 (240 mg, 1.06 mmol) was then added quickly. Stirring was continued for 2 h at -78 °C and the reaction poured into a mixture of a saturated aqueous solution of NH$_4$Cl (5 mL) and H$_2$O (5 mL). The resulting mixture was allowed to warm to rt, extracted with Et$_2$O (20 mL), washed with brine (2 x 10 mL), dried over magnesium sulfate, filtered and concentrated in vacuo. Column chromatography eluting with Et$_2$O (20%)/PE afforded the crude chlorohydrin.

To the crude chlorohydrin in methanol (5 mL) at -10 °C was added K$_2$CO$_3$ (442 mg, 3.2 mmol). The stirring was continued for 4 h until completion and then a saturated aqueous solution of NH$_4$Cl (10 mL) was added. The reaction mixture was extracted with Et$_2$O (2 x 30 mL), washed with brine (2 x 10 mL), dried over magnesium sulfate, filtered and concentrated in vacuo. Flash column chromatography eluting with Et$_2$O (10%)/PE resulted in a pure epoxydiyne 16 (201 mg, 62%).

$\alpha_D^{22}$ +63 (c 1 in CHCl$_3$),

$^\text{1}H$ NMR (300 MHz, CDCl$_3$) $\delta_H$ 4.21 (dd, 1H, J 8.6, 6.7, CHCH$_2$), 4.10 (dd, 1H, J 8.6, 6.2, CHCH$_2$), 4.05 (t, 1H, J 6.4, CHCH$_2$), 3.63 (s, 1H, H$_{\text{epoxy}}$), 2.47 (s, 1H, H$_{\text{alkyne}}$), 1.47 (s, 3H, CH$_3$), 1.35 (s, 3H, CH$_3$), 0.99 (t, 9H, J 7.8, CH$_3$TES), 0.61 (q, 6H, J 7.8, CH$_2$TES);
$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$C 110.9 (C), 99.4 (C), 90.2 (C), 77.1 (C), 75.7 (CH), 75.4 (CH), 66.8 (CH$_2$), 57.8 (C), 49.8 (CH), 26.0 (CH$_3$), 25.1 (CH$_3$), 7.3 (3 x CH$_3$), 4.0 (3 x CH$_2$);

HRMS (M+H)$^+$ cald. for C$_{17}$H$_{27}$O$_3$Si 307.1729, found m/z 307.1725.
(2S,3S,4R)-**tert-**Butyl-[3-(2,2-dimethyl-1,3]dioxolan-4-yl)-3-ethynyl-oxyrany lethynyl]dimethyl-silane 39

![Chemical Structure](image)

To ZnBr₂ (238 mg, 1.06 mmol) in THF (2 mL) at -20 °C was added 175 (100 mg, 0.53 mmol) then the reaction was cooled to -78 °C. A freshly prepared 1 M solution of LDA in THF (1.06 mL, 1.06 mmol) was added dropwise and the reaction was stirred for 1 h. The ketone 35 (119 mg, 0.53 mmol) was then added quickly. Stirring was continued for 2 h at -78 °C and the reaction poured into a mixture of a saturated aqueous solution of NH₄Cl (5 mL) and H₂O (5 mL). The resulting mixture was allowed to warm to rt, extracted with Et₂O (20 mL), washed with brine (2 x 10 mL), dried over magnesium sulfate, filtered and concentrated *in vacuo*. Column chromatography eluting with Et₂O (20%)/PE afforded a crude chlorohydrin.

To the crude chlorohydrin in methanol (5 mL) at -10 °C was added K₂CO₃ (219 mg, 1.59 mmol). The stirring was continued for 4 h until completion and then a saturated aqueous solution of NH₄Cl (10 mL) was added. The reaction mixture was extracted with Et₂O (2 x 30 mL), washed with brine (2 x 10 mL), dried over magnesium sulfate, filtered and concentrated *in vacuo*. Flash column chromatography eluting with Et₂O (5%)/PE resulted in a pure epoxydiyne 39 (99 mg, 61%).

α<sub>D</sub>²² +74 (c 1 in C₆H₆), ¹H NMR (400 MHz, C₆D₆) δ<sub>H</sub> 3.99 (dd, 1H, J 8.8, 6.2, CHCH₂), 3.79 (dd, 1H, J 8.8, 6.6, CHCH₂) 3.64 (t, 1H, J 6.6, CHCH₂) 3.47 (s, 1H, H<sub>epoxy</sub>), 1.98 (s, 1H, H<sub>alkyne</sub>), 1.37 (s, 3H, CH₃), 1.19 (s, 3H, CH₃), 1.03 (s, 9H, C(CH₃)₃), 0.15 (s, 3H, CH₃), 0.14 (s, 3H, CH₃);
$^{13}$C NMR (100 MHz, C<sub>6</sub>D<sub>6</sub>) $\delta$C 110.7 (C), 100.5 (C), 90.6 (C), 78.1 (C), 76.7 (CH), 75.4 (CH), 66.8 (CH<sub>2</sub>), 58.1 (C), 50.1 (CH), 26.2 (4 x CH<sub>3</sub>), 25.4 (CH<sub>3</sub>), 16.7 (C), -4.8 (2 x CH<sub>3</sub>);

HRMS (M+H)$^+$ calcd. for C<sub>17</sub>H<sub>27</sub>O<sub>3</sub>Si 307.1729, found m/z 307.1729.
4-Hydroxy-but-2-ynal diethyl acetal 180\textsuperscript{112}

\[
\begin{array}{c}
\text{HO} \\
\text{==C} \\
\text{OEt} \\
\text{OEt}
\end{array}
\]

To a solution of (propargyloxy)trimethylsilane 179 (30.0 g, 234 mmol) in THF (150 mL) was added a 1 M solution of ethylmagnesium bromide in THF (234 mL, 234 mmol). The reaction was stirred for 30 min and a solution of phenyl orthoformate (41.8 g, 212 mmol) in THF (110 mL) was added. Stirring was continued for 16 h then the reaction quenched with a mixture of a saturated aqueous solution of NH\textsubscript{4}Cl (200 mL) and H\textsubscript{2}O (200 mL), extracted with Et\textsubscript{2}O (2 x 200 mL), washed with NaOH (4 M solution, 3 x 100 mL) dried over magnesium sulfate, filtered and concentrated \textit{in vacuo}. The residue was then dissolved in methanol (530 mL) and K\textsubscript{2}CO\textsubscript{3} (29.3 g, 212 mmol) was added at 0 °C and the mixture stirred for 10 min. The solution was concentrated \textit{in vacuo} then H\textsubscript{2}O (200 mL) was added. The mixture was extracted with EtOAc (3 x 150 mL), dried over magnesium sulfate, filtered and concentrated \textit{in vacuo}. Distillation of the residue under vacuum (bp 88 °C; 1 mmHg) gave 180 (23.7 g, 70%) as a colourless oil.

\(\nu_{\text{max}} \text{ (cm}^{-1}\text{)}\) 3424, 1120;

\(^1\text{H NMR (300 MHz, CDCl}_3\text{)} \delta_\text{H} \text{ 5.26 (d, 1H, } J \text{ 1.3, (EtO)}_2\text{CH), 4.28 (dd, 2H, } J \text{ 6.2, 1.3, CH}_2\text{OH), 3.70 (dq, 2H, } J \text{ 7.2, 9.4, CH}_{2\text{Et}}, \text{ 3.55 (dq, 2H, } J \text{ 7.2, 9.4, CH}_{2\text{Et}}, \text{ 2.30 (br s, 1H, OH), 1.19 (t, 6H, } J \text{ 7.2, CH}_3);}

\(^{13}\text{C NMR (300 MHz; CDCl}_3\text{)} \delta_\text{C} \text{ (75 MHz, CDCl}_3\text{) 91.6 (CH), 84.2 (C), 81.1 (C), 61.3 (CH}_2\text{), 51.1 (CH}_2\text{), 15.4 (CH}_3\text{).}
4-Chloro-1,1-diethoxy-but-2-yne 155*107

\[\text{Cl} \equiv \text{OEt} \quad \text{OEt}\]

To a solution of the alcohol 180 (10.0 g, 63 mmol) and Et₃N (26.4 mL, 190 mmol) in Et₂O (320 mL) was added dropwise methanesulfonyl chloride (5.5 mL, 70 mmol) at 0 °C. Stirring was continued for 1 h and then the reaction quenched with a saturated aqueous solution of NaHCO₃ (120 mL), extracted with Et₂O (2 x 60 mL), dried over magnesium sulfate, filtered and concentrated in vacuo. The residue was dissolved in chloroform (310 mL) with tetra-n-butylammonium chloride (41.0 g, 126 mmol). The reaction was refluxed for 1 h. Concentration of the mixture in vacuo gave the crude residue to which Et₂O (200 mL) was added. The solution was washed with H₂O (100 mL), brine (2 x 100 mL), dried over magnesium sulfate and concentrated in vacuo to give the pure propargylic chloride 155 as a yellow oil (8.9 g, 80%).

ν_{max} (cm⁻¹) 2971, 2901, 2888, 2238;

\(^1\)H NMR (300 MHz, CDCl₃) δ_H 5.23 (t app, 1H, J 1.3, (EtO)₂CH), 4.13 (d, 2H, J 1.3, CH₂Cl), 3.69 (dq, 2H, J 7.2, 9.3, CH₂Et), 3.53 (dq, 2H, J 7.2, 9.3, CH₂Et), 1.18 (t, 6H, J 7.2, CH₃Et);

\(^1\)C NMR (75 MHz, CDCl₃) δ_C 91.1 ((EtO)₂CH), 81.6 (C), 79.9 (C), 60.9 (2 x CH₂Et), 29.7 (CH₂Cl), 14.9 (2 x CH₃Et);

HRMS (M+H)^+ cald. for C₈H₁₄O₂Cl 175.0520, found m/z 175.0518.
(3R),(4S)-4-Chloro-3-((4R)-2,2-dimethyl-[1,3]dioxolan-4-yl)-7,7-diethoxy-1-trimethylsilanyl-hepta-1,5-diyn-3-ol 185 and (3R),(4R)-4-Chloro-3-((4R)-2,2-dimethyl-[1,3]dioxolan-4-yl)-7,7-diethoxy-1-trimethylsilanyl-hepta-1,5-diyn-3-ol 186

To ZnBr₂ (255 mg, 1.1 mmol) in THF (2 mL) at -20 °C was added 155 (100 mg, 0.6 mmol) then the reaction was cooled to -78 °C. A freshly prepared 1 M solution of LDA in THF (1.0 mL, 1.0 mmol) was added dropwise and the reaction was stirred for 1 h. The ketone 35 (118 mg, 0.5 mmol) was then added quickly. Stirring was continued for 2 h at -78 °C and the reaction poured into a mixture of a saturated aqueous solution of NH₄Cl (5 mL) and H₂O (5 mL) then diluted with Et₂O (10 mL). The resulting mixture was allowed to warm to rt and filtered through celite, then extracted with Et₂O (20 mL), washed with brine (2 x 10 mL), dried over magnesium sulfate, filtered and concentrated in vacuo. Column chromatography eluting with Et₂O (20%)/PE afforded the inseparable diastereoisomeric chlorohydrins 185 and 186 (363 mg, anti: syn 10:1, 60%) as a clear yellow oil.

νmax (cm⁻¹) 3400, 2976, 2929, 2895, 2354, 2173, 1450;

¹H NMR (500 MHz, CDCl₃) δH 5.34 (d, 1H, J 1.3, (EtO)₂CH₂sys), 5.32 (d, 1H, J 1.4, (EtO)₂CH₂ann), 4.93 (d, 1H, J 1.4, CHCl₂sys), 4.90 (d, 1H, J 1.4, CHCl₂anti), 4.33 (dd, 1H, 8.5, 5.8, CH₂CH₂sys), 4.32 (dd, 1H, J 6.8, 5.8, CH₂CH₂sys), 4.21 (dd, 1H, J 8.5, 5.8, CH₂CH₂sys), 4.16 (dd, 1H, J 8.5, 6.8, CH₂CH₂sys), 3.727 (dq, 1H, J 9.5, 7.1, CH₂Et₃sys), 3.722 (dq, 1H, J 9.5, 7.1, CH₂Et₃sys), 3.59 (dq, 1H, J 9.5, 7.1, CH₂Et₃sys), 3.58 (dq, 1H, J 9.5, 7.1, CH₂Et₃sys), 2.86 (s, 1H, OH₂sys), 2.84 (s, 1H, OH₂sys), 1.44 (s, 3H, CH₃), 1.32 (s, 3H, CH₃), 1.22 (t, 3H, J 7.2, CH₃sys), 1.21 (t, 3H, J 7.2, CH₃sys), 0.17 (s, 9H, SiCH₃);
$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta_C$ 110.4 (Me$_2$C$_{anti}$), 110.3 (Me$_2$C$_{syn}$), 101.5 (C$_{anti}$), 101.3 (C$_{syn}$), 93.6 (C$_{syn}$), 92.7 (C$_{anti}$), 90.99 ((EtO)$_2$CH$_{anti}$), 90.95 ((EtO)$_2$CH$_{syn}$), 84.1 (C$_{anti}$), 83.3 (C$_{syn}$), 80.3 (C$_{syn}$), 78.9 (C$_{anti}$), 77.6 (CH$_{anti}$), 76.3 (CH$_{syn}$), 74.9 (COH$_{anti}$), 74.3 (COH$_{syn}$), 66.8 (CH$_2$$_{anti}$), 66.3 (CH$_2$$_{syn}$), 60.9 (CH$_2$Et$_{anti}$), 60.8 (CH$_2$Et$_{syn}$), 60.8 (CH$_2$Et$_{syn}$), 60.9 (CH$_2$Et$_{anti}$), 55.0 (CH$_3$Cl$_{anti}$), 53.7 (CH$_3$Cl$_{syn}$), 26.2 (CH$_3$$_{anti}$), 26.1 (CH$_3$$_{syn}$), 25.2 (CH$_3$$_{anti}$), 25.1 (CH$_3$$_{syn}$), 14.914 (CH$_3$Et$_{anti}$), 14.912 (CH$_3$Et$_{syn}$), -0.53 (3 x CH$_3$$_{anti}$), -0.57 (3 x CH$_3$$_{syn}$);

HRMS (M+NH$_4$)$^+$ cald. for C$_{19}$H$_{35}$NO$_5$Cl 420.1968, found $m/z$ 420.1970.
(2S,3S,4R)-4-[3-(3,3-Diethoxy-prop-1-ynyl)-2-ethynyl-oxyranyl]-2,2-dimethyl-[1,3]dioxolane 73\textsuperscript{107} and 187\textsuperscript{107}

\[
\begin{align*}
\text{trans 73} & \quad \text{cis 187}
\end{align*}
\]

To ZnBr\textsubscript{2} (255 mg, 1.1 mmol) in THF (2 mL) at -20 °C was added 155 (100 mg, 0.6 mmol) then the reaction was cooled to -78 °C. A freshly prepared 1 M solution of LDA in THF (1.0 mL, 1.0 mmol) was added dropwise and the reaction was stirred for 1 h. The ketone 35 (118 mg, 0.5 mmol) was then added quickly. Stirring was continued for 2 h at -78 °C and the reaction poured into a mixture of a saturated aqueous solution of NH\textsubscript{4}Cl (5 mL) and H\textsubscript{2}O (5 mL) then diluted with Et\textsubscript{2}O (10 mL). The resulting mixture was allowed to warm to rt and filtered through celite, then extracted with Et\textsubscript{2}O (20 mL), washed with brine (2 x 10 mL), dried over magnesium sulfate, filtered and concentrated \textit{in vacuo} to give the crude diastereoisomeric chlorohydrins.

To the crude chlorohydrins in DMF (3 mL) was added KF (263 mg, 2.0 mmol). The reaction mixture was stirred overnight and both ether (40 mL) and a saturated aqueous solution of NH\textsubscript{4}Cl (30 mL) were added. The aqueous layer was washed with Et\textsubscript{2}O (2 x 15 mL) and the combined organic extracts washed with H\textsubscript{2}O (2 x 20 mL), brine (20 mL), dried over magnesium sulfate, filtered and concentrated \textit{in vacuo}. Column chromatography eluting with Et\textsubscript{2}O (20%)/PE afforded the \textit{trans}-epoxydiyne 73 (97 mg, 66%) and the \textit{cis}-epoxydiyne 187 (10 mg, 7%).
α_d^22 +30.2 (c 0.508 in CHCl_3, 589 nm, trans-epoxydiyne);
α_d^22 -61.2 (c 1 in CHCl_3, 589 nm, cis-epoxydiyne);
v_{max} (cm^{-1}) 3201,2926, 2854, 2195, 2160,1399,1273,1210,1087;

trans-epoxydiyne:

^1H NMR (500 MHz, CDCl_3) δ_H 5.29 (1H, d, J 1.1, (EtO)_2CH), 4.18 (1H, dd, J 10.8, 8.9, CHCH_2), 4.065 (1H, dd, J 10.8, 5.9, CHCH_2), 4.062 (1H, dd, J 8.9, 5.9, CHCH_2), 3.75 (1H, dq, J 9.6, 7.0, H_C), 3.73 (1H, dq, J 9.6, 7.0, H_C'), 3.68 (1H, dd, J 1.1, H_{epoxy}), 3.57 (2H, dq, J 9.4, 7.0, H_D and H_{D'}), 2.47 (1H, s, H_alkyne), 1.42 (3H, s, CH_3), 1.32 (3H, s, CH_3), 1.25 (3H, t, J 7.0, CH_3Et), 1.20 (3H, t, J 7.0, CH_3Et);

^13C NMR (125 MHz, CDCl_3) δ_C 111.0 (Me_2C), 91.0 ((EtO)_2CH), 81.8 (C), 78.8 (C), 77.0 (C), 75.6 (CH_alkyne), 75.4 (CH), 66.7 (CH_2), 61.1 (CH_2Et), 61.0 (CH_2Et), 57.7 (C_{epoxy}), 49.1 (CH_{epoxy}), 25.9 (CH_3), 25.0 (CH_3), 15.2 (CH_3Et), 15.0 (CH_3Et);

cis-epoxydiyne:

^1H NMR (500 MHz, CDCl_3) δ_H 5.20 (1H, d, J 1.1, (EtO)_2CH), 4.12 (1H, dd, J 8.7, 6.3,CHCH_2), 4.11 (1H, dd, J 8.75, 6.3, CHCH_2), 3.98 (1H, t, J 6.2, CHCH_2), 3.71 (1H, d, J 1.1, H_{epoxy}), 3.64 (1H, dq, J 9.5, 7.0, H_C), 3.63 (1H, dq, J 9.5, 7.0, H_C'), 3.506 (1H, dq, J 9.5, 7.0, H_D), 3.502 (1H, dq, J 9.5, 7.0, H_{D'}), 2.38 (1H, s, H_alkyne), 1.42 (3H, s, CH_3), 1.32 (3H, s, CH_3), 1.14 (3H, t, J 7.0, CH_3Et), 1.13 (3H, t, J 7.0, CH_3Et);

^13C NMR (125 MHz, CDCl_3) δ_C 110.6 (Me_2C), 90.8 ((EtO)_2CH), 82.4 (C), 77.7 (C), 77.5 (C), 75.1 (CH), 73.8 (CH_alkyne), 66.5 (CH_2), 60.8 (CH_2Et), 60.7 (CH_2Et), 55.6 (C_{epoxy}), 51.4 (CH_{epoxy}), 25.9 (CH_3), 25.1 (CH_3), 14.8 (2 x CH_3);

HRMS (M+NH_4)^+ calcd. for C_{16}H_{26}NO_5 312.1805, found m/z 312.1805.
(2R)-1-(1,4-Dioxo-spiro[4.5]dec-2-yl)-3-trimethylsilyl-prop-2-yn-1-ol 196

To a solution of 1,2-5,6-Di-O-cyclohexyldene-β-mannitol 194 (25.0 g, 73 mmol) in MeCN/H₂O (145 mL:95 mL) was added portionwise sodium periodate (31 g, 146 mmol) over 20 min and the reaction mixture was stirred for 2 h. The reaction mixture was extracted with ether, dried over magnesium sulfate and concentrated in vacuo.

Meanwhile to a solution of trimethylsilylacetylene (24 mL, 175 mmol) in THF (900 mL) was added freshly made lithium hexamethyldisilazide (192 mL, 192 mmol) at –78 °C. The reaction mixture was stirred for 30 min and a solution of 195 (24.8 g, 146 mmol) in THF (250 mL) was added over a period of 30 min. The reaction was stirred for 30 min and quenched by the addition of saturated aqueous NH₄Cl (150 mL). The reaction mixture was concentrated in vacuo to a volume of approximately 300 mL and diluted with EtOAc (300 mL). The mixture was washed with a saturated aqueous solution of NH₄Cl (250 mL) and H₂O (250 mL), and the combined aqueous portions were extracted with EtOAc (150 mL). The organics were washed with brine (100 mL), dried over magnesium sulfate, filtered and concentrated in vacuo. Flash column chromatography in EtOAc (20%)/PE afforded the inseparable diastereomeric propargylic alcohols 196 (1:1, 22.7 g, 58%) as a pale yellow oil.

vmax (cm⁻¹) 3431, 2932, 2903, 2853, 2173;

¹H NMR (300 MHz; CDCl₃) δH 4.35-3.71 (m, 4H, CH₂O-CHO-CHOH), 2.40 (1H, d, J 3.9, OH), 2.25 (1H, d, J 4.8, OH, other diastereoisomer), 1.51-1.29 (m, 10H, CH₂cyclohexyl), 0.01 (s, 9H, CH₃);

¹³C NMR (75 MHz; CDCl₃) δC 111.4 (C_cyclohexyl), 111.0 (C_cyclohexyl), 102.6 (C), 102.5 (C), 91.8 (C), 91.7 (C), 78.7 (CH₂OH), 77.7 (CH₂OH), 66.1 (CH₂), 65.3 (CH₂), 65.0 (CH), 63.1 (CH), 36.8 (CH₂cyclohexyl), 36.2 (CH₂cyclohexyl), 35.1 (CH₂cyclohexyl), 35.0
(CH\textsubscript{2}cyclohexyl), 25.4 (CH\textsubscript{2}cyclohexyl), 25.3 (CH\textsubscript{2}cyclohexyl), 24.2 (2 x CH\textsubscript{2}cyclohexyl), 24.0 (2 x CH\textsubscript{2}cyclohexyl), 0.0 (6 x (CH\textsubscript{3}));

HRMS (M+H)\textsuperscript{+} cald. for C\textsubscript{14}H\textsubscript{25}O\textsubscript{3}Si 269.1567, found m/z 269.1570.
(2R)-1-(1,4-Dioxo-spiro[4.5]dec-2-yl)-3-trimethylsilyl-propynone 197

Method A: To pyridinium dichromate (2.8 g, 7.5 mmol) and crushed 3Å molecular sieves (1.7 g) in DCM (7 mL) was added dropwise a solution of propargylic alcohol 196 (1.0 g, 3.7 mmol) in DCM (3.5 mL) and the reaction mixture was stirred for 4 h. Celite (2 g) was added and the suspension was stirred for 30 min. The reaction mixture was then filtered through a plug of celite and diluted with ether (100 mL). The filtrate was washed with saturated aqueous potassium hydrogen sulphate (3 x 5 mL), saturated aqueous NaHCO₃ (5 mL) and brine (2 x 10 mL), then dried over magnesium sulfate, filtered and concentrated in vacuo. Flash column chromatography eluting with Et₂O (10%)/PE afforded the ynone 197 (0.512 g, 38%).

Method B: To 196 (5.0 g, 18.6 mmol) in DCM (93 mL) at 0 °C was added Dess-Martin periodinane (15.5 g, 37.2 mmol) in one portion. The stirring was continued at rt for 12 h and the reaction mixture was poured into a mixture of a saturated aqueous solution of sodium thiosulfate (10 mL) and a saturated aqueous solution of NaHCO₃ (10 mL). Then Et₂O (150 mL) was added and the mixture stirred for 30 min. The mixture was extracted with Et₂O, washed with brine, dried over magnesium sulfate, filtered and concentrated in vacuo. Flash column chromatography eluting with Et₂O (10%)/PE afforded the pure ynone 197 (4.6 g, 94%). Alternatively the crude propargylic ketone, which was seen to be of sufficient purity (without flash chromatography) for use in further stages, was stored at -20 °C for later use.
vmax (cm$^{-1}$) 2932, 2862, 2150, 1677, 1399, 1372;

$^1$H NMR (300 MHz, CDCl$_3$) δ$_H$ 4.33 (1H, dd, $J$ 7.3, 4.6, CHCH$_2$), 4.05 (1H, dd, $J$ 8.6, 7.3, CHCH$_2$), 3.97 ((1H, dd, $J$ 8.6, 4.6, CHCH$_2$), 1.74-1.36 (m, 10H, CH$_2$ cyclohexyl), 0.07 (s, 9H, CH$_3$);

$^{13}$C NMR (75 MHz, CDCl$_3$) δ$_C$ 187.0 (C=O), 113.4 (C), 104.4 (C), 100.6 (C), 81.5 (CH), 67.5 (CH$_2$), 36.5 (CH$_2$ cyclohexyl), 35.9 (CH$_2$ cyclohexyl), 25.9 (CH$_2$ cyclohexyl), 24.8 (CH$_2$ cyclohexyl), 24.7 (CH$_2$ cyclohexyl), 0.0 (3 x CH$_3$);

HRMS (M+H)$^+$ calcd. for C$_{14}$H$_{23}$O$_3$Si 267.1411, found m/z 267.1413.
(2R,3R,4S)-4-Choro-3-(1,4-dioxaspiro[4.5]deca-2-yl)-7,7-diethoxy-1-trimethylsilylhepta-1,5-diyne-3-ol 197 and (2R,3R,4R)-4-Choro-3-(1,4-dioxaspiro[4.5]deca-2-yl)-7,7-diethoxy-1-trimethylsilylhepta-1,5-diyne-3-ol 198

To ZnBr₂ (2.2 g, 9.8 mmol) in THF (9 mL) at -20 °C was added 155 (0.8 g, 4.7 mmol) then the reaction was cooled to -78 °C. A freshly prepared 1 M solution of LDA in THF (9.3 mL, 9.3 mmol) was added dropwise and the reaction was stirred for 1 h. The ketone 35 (1.2 g, 4.6 mmol) was then added quickly. Stirring was continued for 3 h at -78 °C and the reaction was poured into a mixture of a saturated aqueous solution of NH₄Cl (4 mL) and H₂O (50 mL), then diluted with Et₂O (150 mL). The resulting mixture was allowed to warm to rt and filtered through celite, then extracted with Et₂O (50 mL), washed with brine (2 x 30 mL), dried over magnesium sulfate, filtrated and concentrated in vacuo. Column chromatography eluting with Et₂O (20%)/PE afforded the inseparable diastereomeric chlorohydrins 197 and 198 (1.4 g, anti:syn 5/1, 59%) as a clear yellow oil.

vmax (cm⁻¹) 3402, 2932, 2895, 2866, 2252, 2173, 1446, 1380, 1250;

¹H NMR (400 MHz, CDCl₃) δ (d, 1H, J 1.3, (EtO)₂CH₃[x], 5.32 (d, 1H, J 1.4, (EtO)₂CH₃[y]); 4.96 (d, 1H, J 1.3, CHCl₃[x]); 4.93 (d, 1H, J 1.4, CHCl₃[y]); 4.32 (dd, 1H, J 6.8, 5.9, CH₂CH₃[x]); 4.30 (dd, 1H, J 6.8, 5.9, CH₂CH₃[y]); 4.20 (dd, 1H, J 8.5, 6.8, CH₂CH₃[x]); 4.19 (dd, 1H, J 8.5, 5.9, CH₂CH₃[y]); 4.16 (dd, 1H, J 8.5, 6.8, CH₂CH₃[x]); 4.14 (dd, 1H, J 8.5, 6.8, CH₂CH₃[y]); 3.77-3.67 (m, 2H, CH₃); 3.53-3.64 (m, 2H, CH₃); 2.94 (s, 1H, OH₃); 2.86 (s, 1H, OH₃); 1.72-1.65 (m, 2H, CH₂cyclohexyl); 1.62-1.49 (m, 6H, CH₂cyclohexyl); 1.42-1.32 (m, 2H, CH₂cyclohexyl); 1.23 (t,
$^3$H, $J$ 7.0, CH$_3$Et$_{syn}$), 1.22 (t, 3H, $J$ 7.1, CH$_3$Et$_{anti}$), 1.22 (t, 3H, $J$ 7.1, CH$_3$Et$_{anti}$), 1.21 (t, 3H, $J$ 7.1, CH$_3$Et$_{anti}$), 0.16 (s, 9H, SiCH$_3$);

$^{13}$C NMR (100 MHz, CDCl$_3$) δ C 111.0 (C$_{cyclohexyl}$)$_{anti}$, 110.9 (C$_{cyclohexyl}$)$_{syn}$, 101.8 (C$_{anti}$), 101.5 (C$_{syn}$), 93.7 (C$_{syn}$), 92.7 (C$_{anti}$), 91.1 ((EtO)$_2$CH$_{anti}$), 91.0 ((EtO)$_2$CH$_{syn}$) 84.2 (C$_{anti}$), 83.5 (C$_{syn}$), 80.4 (C$_{syn}$), 79.1 (C$_{anti}$), 77.2 (CH$_{anti}$), 76.1 (CH$_{syn}$), 75.2 (C$_{OH}$)$_{syn}$), 74.6 (C$_{OH}$)$_{syn}$), 66.6 (CH$_2$)$_{anti}$, 66.1 (CH$_2$)$_{syn}$), 61.0 (CH$_2$)$_{anti}$, 60.97 (CH$_2$)$_{syn}$), 60.94 (CH$_2$)$_{syn}$), 60.8 (CH$_2$)$_{anti}$), 55.3 (CH$_{Cl}$)$_{anti}$), 53.9 (CH$_{Cl}$)$_{syn}$), 35.9 (CH$_2$)$_{cyclohexyl}$), 34.9 (CH$_2$)$_{cyclohexyl}$), 25.10 (CH$_2$)$_{cyclohexyl}$), 23.8 (CH$_2$)$_{cyclohexyl}$), 23.7 (CH$_2$)$_{cyclohexyl}$), 15.0 (2 x CH$_3$)$_{E}$), -0.3 (3 x CH$_3$)$_{syn}$), -0.4 (3 x CH$_3$)$_{anti}$);

HRMS (M+NH$_4$)$^+$ cald. for C$_{22}$H$_{39}$ClNO$_3$Si 460.2281, found m/z 460.2279.
(2R,3S)-2-[3-(3,3)-Diethoxy-pro-1-ynyl)-(2S)-2-ethynyl-oxiranyl]-1,4-dioxaspiro[4.5]decane 199 and 200

trans 199
cis 200

To ZnBr₂ (2.2 g, 9.8 mmol) in THF (9 mL) at -20 °C was added 155 (0.8 g, 4.7 mmol) then the reaction was cooled to -78 °C. A freshly prepared 1 M solution of LDA in THF (9.3 mL, 9.3 mmol) was added dropwise and the reaction was stirred for 1 h. The ketone 35 (1.2 g, 4.6 mmol) was then added quickly. Stirring was continued for 3 h at -78 °C and the reaction was poured into a mixture of a saturated aqueous solution of NH₄Cl (4 mL) and H₂O (50 mL) then diluted with Et₂O (150 mL). The resulting mixture was was to warm to rt and filtered through celite, then extracted with Et₂O (50 mL), washed with brine (2 x 30 mL), dried over magnesium sulfate, filtered and concentrated in vacuo to give the crude diastereoisomeric chlorohydrins.

To the crude chlorohydrins in DMF (30 mL) was added KF (1.9 g, 18.4 mmol). The reaction mixture was stirred overnight and both Et₂O (40 mL) and a saturated aqueous solution of NH₄Cl (30 mL) were added. The aqueous layer was extracted with Et₂O (2 x 15 mL) and the combined organic extracts washed with H₂O (2 x 20 mL), brine (20 mL), dried over magnesium sulfate, filtered and concentrated in vacuo. Column chromatography eluting with Et₂O (20%)/PE afforded the trans-epoxydiyne 199 (953 mg, 62%) and the cis epoxydiyne 200 (184 mg, 12%).

$$\alpha_D^{22} +30.2 \ (c \ 0.508 \ \text{in CHCl}_3, \ 589 \ \text{nm}, \ \text{trans epoxydiyne})$$;

$$\alpha_D^{22} -61.2 \ (c \ 1 \ \text{in CHCl}_3, \ 589 \ \text{nm}, \ \text{cis epoxydiyne})$$;

vmax (cm⁻¹) 3205, 2940, 2841, 2180, 2160;

**trans-epoxydiyne:**
$^1$H NMR (500 MHz, CDCl$_3$) $\delta_H$ 5.30 (d, 1H, J 0.9, (EtO)$_2$CH), 4.19 (dd, 1H, J 11.0, 9.2, CHCH$_2$), 4.065 (dd, 1H, J 10.8, 5.9, CHCH$_2$), 4.062 (dd, 1H, J 8.9, 5.9, CHCH$_2$), 3.757 (dq, 1H, J 9.5, 7.0, CHC), 3.750 (dq, 1H, J 9.5, 7.0, CHC), 3.71 (dd, 1H, J 0.9, $H_{\text{epoxy}}$), 3.58 (dq, 2H, J 9.4, 7.0, $H_D$ and $H_D'$), 2.48 (s, 1H, H$_{\text{alkyne}}$), 1.72-1.65 (m, 2H, CH$_2$cyeloxy), 1.63-1.50 (m, 6H, CH$_2$cyeloxy), 1.41-1.31 (m, 2H, CH$_2$cyeloxy), 1.219 (t, 3H, J 7.0, CH$_3$Et), 1.214 (t, 3H, J 7.0, CH$_3$Et);

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta_C$ 111.6 (C$_{\text{cyeloxy}}$), 91.0 ((EtO)$_2$C), 81.6 (C), 78.8 (C), 77.0 (C), 75.5 (CH$_{\text{alkyne}}$), 75.0 (CH), 66.3 (CH$_2$) 61.0 (CH$_2$Et$_3$), 60.9 (CH$_2$Et$_3$), 57.8 (C$_{\text{epoxy}}$), 49.0 (C$_{\text{epoxy}}$), 35.4 (CH$_2$cyeloxy), 34.4 (CH$_2$cyeloxy), 24.8 (CH$_2$cyeloxy), 23.7 (CH$_2$cyeloxy), 23.5 (CH$_2$cyeloxy), 14.932 (CH$_3$Et), 14.931 (CH$_3$Et);

**cis-epoxydiyne:**

$^1$H NMR (500 MHz, CDCl$_3$) $\delta_H$ 5.27 (1H, d, J 0.9, (EtO)$_2$CH), 4.17 (1H, dd, J 8.7, 6.5, CHCH$_2$), 4.16 (1H, dd, J 8.7, 6.5, CHCH$_2$), 4.04 (1H, t, J 6.5, CHCH$_2$), 3.78 (1H, d, J 0.9, $H_{\text{epoxy}}$), 3.71 (1H, dq, J 9.4, 7.1, CHC), 3.70 (1H, dq, J 9.4, 7.1, CHC$^+$), 3.57 (1H, dq, J 9.4, 7.1, H$_D$), 3.56 (1H, dq, J 9.4, 7.1, H$_D'$), 2.38 (1H, s, H$_{\text{alkyne}}$), 1.72-1.65 (m, 2H, CH$_2$cyeloxy), 1.62-1.49 (m, 6H, CH$_2$cyeloxy), 1.42-1.32 (m, 2H, CH$_2$cyeloxy), 1.21 (3H, t, J 7.1, CH$_3$Et), 1.20 (3H, t, J 7.1, CH$_3$Et);

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta_C$ 111.3 (C$_{\text{cyeloxy}}$), 90.9 ((EtO)$_2$CH), 82.4 (C), 77.9 (C), 77.7 (C), 74.7 (C), 73.8 (CH$_{\text{alkyne}}$), 66.2 (CH$_2$), 61.0 (CH$_2$Et$_3$), 60.9 (CH$_2$Et$_3$), 55.8 (C$_{\text{epoxy}}$), 51.6 (CH$_{\text{epoxy}}$), 35.5 (CH$_2$cyeloxy), 34.7 (CH$_2$cyeloxy), 25.0 (CH$_2$cyeloxy), 23.7 (CH$_2$cyeloxy), 23.6 (CH$_2$cyeloxy), 14.915 (CH$_3$Et), 14.914 (CH$_3$Et);

HRMS (M+N$_4$H$^+$) calcd. for C$_{19}$H$_{30}$N$O_5$ 352.2118, found m/z 352.2118.
(4S,5R)-2-Bromo-5-(‘butyl-dimethyl-silanyloxy)-4-hydroxy-cyclopent-2-enone

To cyclopentenone 72 (3.0 g, 13.1 mmol) in DCM (66 mL) at 0 °C was added bromine (0.75 mL, 14.4 mmol) dropwise. After 10 min Et$_3$N (11.41 mL, 80.0 mmol) was added dropwise. The reaction mixture was allowed to warm to rt and stirred for 1 h. The reaction was then quenched with H$_2$O (80 mL), extracted with Et$_2$O (3 x 60 mL), washed with brine (2 x 50 mL), dried over magnesium sulfate, filtered and concentrated in vacuo. Flash column chromatography eluting with Et$_2$O (15%)/PE afforded 208 (3.92 g, 97%) as a colourless oil.

v$_{max}$ (cm$^{-1}$) 3424, 2978, 2858, 1724, 1360;

$^1$H (300MHz, CDCl$_3$, J (Hz)) $\delta$$_H$ (ppm) 7.50 (d, 1H, $J$ 2.4, CH$_{alkene}$), 4.70 (m, 1H, CHOTBS), 4.20 (d, 1H, $J$ 2.4, CH$_{OH}$), 2.59 (br s, 1H, OH), 0.93 (s, 9H, C(CH$_3$)$_3$), 0.19 (s, 3H, SiCH$_3$), 0.16 (s, 3H, SiCH$_3$);

$^{13}$C (75MHz, CDCl$_3$) $\delta$$_C$ (ppm) 196.1 (C=O), 158.6 (CH$_{alkene}$), 125.2 (C$_{Br}$), 80.8 (CH$_{OTBS}$), 77.1 (CH$_{OH}$), 25.7 (3 x CH$_3$), 18.3 (C), -4.5 (CH$_3$), -5.1 (CH$_3$).
(1R,2S,3S)-2-[1,2-Bis-(tert-butyl-dimethyl-silanyloxy)-ethyl]-2-ethynyl-3-triethylsilanylethynyl-oxirane 210

To a solution of the epoxy-alcohol 209 (0.100 mg, 0.26 mmol) and Et₃N (0.1 mL, 0.78 mmol) in DCM (1.3 mL) was added TBSCI (78 mg, 0.52 mmol) at rt. Stirring was continued for 4 h and then the reaction quenched with a saturated aqueous solution of NaHCO₃ (1 mL). The aqueous layer was extracted with Et₂O (2 x 5 mL), dried over magnesium sulfate, filtered and concentrated in vacuo. Column chromatography eluting with Et₂O (5%)/PE afforded the title compound 210 (118 mg, 92%) as a white solid.

vmax (cm⁻¹) 3280, 2960, 2929, 2882, 2183, 2127, 1463, 1369, 1256;

¹H NMR (300 MHz, CDCl₃) δH 3.89-3.73 (m, 3H, CHCH₂), 3.61 (s, 1H, Hₐpox), 2.42 (s, 1H, C=CH), 0.99 (t, 9H, J 7.2, CH₃TES), 0.89 (s, 9H, CH₃CₜBS), 0.86 (s, 9H, CH₃CₜBS), 0.61 (q, 6H, J 7.2, CH₂TES), 0.05 (s, 12H, CH₃SiₜBS);

¹³C NMR (75 MHz, CDCl₃) δC 100.7 (CTES), 89.0 (C), 78.8 (C), 74.7 (CHₐlkyne), 72.6 (CH), 65.2 (CH₂), 57.7 (Cₐpox), 47.7 (Cₐpox), 25.9 (3 x CH₃), 25.7 (3 x CH₃), 18.2 (CₜBS), 18.2 (CₜBS), 7.3 (3 x CH₃TES), 4.1 (3 x CH₂TES), -4.8 (2 x CH₃TES), -4.9 (2 x CH₃TES);

HRMS (M+Na)⁺ calcd. for C₂₆H₅₉O₃Si₃Na 518.3038, found m/z 518.3052.
(1R,2S,3S,4S,5R)-3-{2-[1,2-Bis-(tert-butyl-dimethyl-silyloxy)-ethyl]-3-triethylsilanylethynyl-oxiranylethynyl]-2-bromo-5-(tert-butyl-dimethyl-silyloxy)-4-hydroxy-cyclopentenone 212

To a solution of 210 (40 mg, 0.080 mmol) in THF (0.5 mL) was added a 2.3 M solution of nBuLi in hexanes (0.038 mL) at -78 °C. After 40 min, Et₃N (11.2 μL) was added followed by addition of a 1M solution of dimethylaluminium chloride in THF (105.0 μL) and the reaction mixture was warm at rt and stirred for 1h. A solution of enone 208 (12.5 mg, 0.040 mmol) in THF (0.3 mL) with activated molecular sieves 4Å (5 mg) was then added via canula to the reaction mixture at -45 °C. The reaction was stirred for 2h at this temperature and quenched with Rochelle’s salt (1 mL), extracted with EtOAc (3 x 2 mL), dried over magnesium sulfate, filtered and concentrated in vacuo. Flash column chromatography eluting with Et₂O (15%)/PE afforded 215 (3.2 mg, 10%) as a colourless oil.

νmax (cm⁻¹) 3664, 2950, 1757, 2130, 2105; ¹H NMR (500 MHz, CDCl₃) δH 4.36 (d, 1H, J 9.54, CHBr), 4.12 (m, 1H, CH(OTBS)cyclopentanone), 4.02 (m, 1H, CHHCHOTBS), 3.88 (m, 2H, CHHCHOTBS), 3.81 (dd, 1H, J 4.01, 1.46, CHOH), 3.69 (s, 1H, Hepoxy), 3.51 (dd, 1H, J 9.54, 4.01, CHCHBr), 2.64 (s, 1H, OH), 0.97 (t, 9H, J 7.8, CH₃TES), 0.88 (s, 9H, SiC(CH₃)₃), 0.878 (s, 9H, SiC(CH₃)₃), 0.0870 (s, 9H, SiC(CH₃)₃), 0.61 (q, 6H, J 7.8, CH₂TES), 0.14 (s, 3H, CH₃TEScyclopentanone), 0.12 (s, 3H, CH₃TEScyclopentanone), 0.067 (s, 12H, CH₃TBS); ¹³C NMR (125 MHz, CDCl₃) δC 205.9 (C=O), 100.78 (CTES), 77.2 (CHOTBScyclopentanone), 76.9 (C), 76.8 (C), 76.7 (C), 75.5 (CHOH), 72.5 (CHdione), 65.4 (CH₂), 57.9 (Cepoxy), 48.3 (CHepoxy), 47.0 (CHBr), 43.4 (CHCHBr), 25.8 (3 x CH₃TBS),
25.6 (3 x CH\textsubscript{3}TBS), 25.5 (3 x CH\textsubscript{3}TBS), 18.7 (3 x C\textsubscript{TBS}), 7.3 (3 x CH\textsubscript{3}TES), 4.0 (3 x CH\textsubscript{2}TES), -4.9 (2 x CH\textsubscript{3}TBS), -5.2 (2 x CH\textsubscript{3}TBS), -5.4 (2 x CH\textsubscript{3}TBS);
HRMS (M+NH\textsubscript{4})\textsuperscript{+} cald. for C\textsubscript{37}H\textsubscript{75}O\textsubscript{6}NSi\textsubscript{4} 818.3693, found m/z 818.3688.
(4S,5R)-2,2-Dimethyl-propionic acid5-(tert-butyl-dimethyl-silanyloxy)-4-oxo-cyclopent-2-enyl ester 215

To cyclopentenone 72 (100 mg, 0.44 mmol) in DCM (1.45 mL) at 0 °C was added Et₃N (0.122 mL, 0.88 mmol). After 10 min pivaloyl chloride (0.060 mL, 0.48 mmol) was added dropwise. The reaction mixture was allowed to warm to rt and stirred for 2 h. The reaction was then quenched with a saturated aqueous solution of NaHCO₃ (2 mL), extracted with Et₂O (3 x 6 mL), washed with brine (2 x 1 mL), dried over magnesium sulfate, filtered and concentrated in vacuo. Flash column chromatography eluting with Et₂O (5%)/PE afforded 215 (126 mg, 92%) as a colourless oil.

vmax (cm⁻¹) 2935, 2887, 2862, 1737, 1619, 1471;
¹H (300 MHz, CDCl₃) δH 7.30 (dd, 1H, J 6.2, CH₆alkene), 6.27 (d, 1H, J 6.2, CH₆alkene), 5.61 (d, 1H, J 1.2, CHOTBS), 4.07 (d, 1H, J 2.9, CHOPiv), 1.21 (s, 9H, C(CH₃)₃), 0.88 (s, 9H, SiC(CH₃)₃), 0.14 (s, 3H, CH₃Si), 0.10 (s, 3H, CH₃Si);
¹³C (75 MHz, CDCl₃) δC 201.6 (C=O), 177. 8 (C=O), 155.5 (CH), 134.0 (CH), 78.8 (CH), 78.0 (CH), 38.7 (C), 27.0 (3 x CH₃), 25.6 (3 x CH₃), 18.2 (C₆TBS), -4.5 (CH₃TBS), -5.2 (CH₃TBS);
HRMS (M+H)⁺ calcd. for C₁₆H₂₉O₄Si 313.1829, found 313.1809.
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6 PUBLICATIONS
